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SYMPOSIUM ON THE MANAGEMENT OF HEMATOLOGIC DISORDERS

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SOME IMPLICATIONS OF MORTALITY STATISTICS RELATING TO CORONARY ARTERY DISEASE

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NEW YORK, N. Y.

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IT IS my purpose to present mortality statistics and other data that shed light on the trend of death rates from coronary artery disease and to discuss the variations in mortality from this disease by sex, race, marital status, geographic region, socioeconomic status, and other factors. My principal conclusion is that the real increase in mortality from this disease during the past fifteen years has been relatively small, certainly not of the magnitude to justify the alarms expressed in the press and elsewhere. I will also endeavor to summarize the evidence which indicates that both the level and the trend of mortality from this disease have been influenced by a number of seemingly unrelated factors.

TREND OF DEATH RATE FROM CORONARY ARTERY DISEASE

The main hindrance in unraveling the trend of mortality from coronary artery disease stems from the radical changes introduced in 1949 in the procedures and the classifications used for recording causes of death. These changes invalidate direct comparisons between the death rates from coronary disease prior to 1949 and those recorded since then. Even more difficult to appraise is the effect on recorded death rates from coronary disease of such developments as the gradual acceptance of a broader concept of coronary disease, better diagnosis of the disease, and increasing resort to this diagnosis by coroners and medical examiners in cases of sudden death or where the deceased had not received medical attention.

Before 1949, when several diseases were reported on a death certificate, then, irrespective of the order in which a physician listed them, the death was assigned to a particular cause according to more or less arbitrary rules of procedure embodied in the Manual of Joint Causes of Death. Under these rules, coro-

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nary disease when certified jointly with chronic myocardial or hypertensive diseases, diabetes, nephritis, cancer, and other diseases was not considered as the primary cause of death and was, therefore, not counted as a death from coronary disease in tabulations of death by cause. Furthermore, the diagnosis of arteriosclerotic heart disease was then classified in the category of myocardial disease, which category also included hypertensive heart disease and a number of other descriptive terms.

With the introduction of the Sixth Revision of the International List of Causes of Death in 1949, a new form of death certificate, as well as new procedures and classifications, was adopted. In the new form the certifying physician is required to indicate the underlying disease to which the death should be ascribed. If the physician lists coronary disease as the underlying cause, the death is so recorded irrespective of any concurrent diseases mentioned as contributory causes. Furthermore, clinicians have come to accept a broader concept of arteriosclerotic heart disease as more significant for classification than the diagnosis of coronary artery disease or its symptoms. Accordingly, the fundamental classification established under the Sixth Revision of the International List was arteriosclerotic heart disease including coronary disease (Code 420), and was composed of three main subdivisions.

420.0 Arteriosclerotic heart disease, so described (with or without mention of coronary disease or angina pectoris).
420.1 Heart disease specified as involving coronary arteries.
420.2 Angina pectoris without mention of coronary disease.

Whenever a diagnosis of any form of arteriosclerotic heart disease included in Code 420 appears on the death certificate with myocardial or hypertensive disease or with arteriosclerosis, the death is classified under the appropriate subdivision of Code 420, even though the physician may certify the myocardial or hypertensive disease or the arteriosclerosis as the underlying cause.

It is not possible to make reasonably accurate estimates of the number of deaths which would have been reported under the newer and broader concept of arteriosclerotic heart disease during the years before 1949. However, it is feasible to estimate the number of deaths which would have been classified as coronary artery disease (including angina pectoris—essentially title 94 of the Fifth Revision) during the years 1940 through 1948 if the Sixth Revision of the International List of Causes of Death had been in use at that time. One estimate made in the Metropolitan Life Insurance Company from a review of the deaths in the general population assigned to coronary artery disease in 1948 and 1949 indicated that the effect of the Sixth Revision was to raise coronary disease death rates by about 25 per cent for white males and about 35 per cent for white females. An independent estimate, based on a 10 per cent sample of the 1949 death certificates, made in the National Office of Vital Statistics[1] pointed to an increase of about 25 per cent for the total population.

The recorded death rates from coronary disease (including angina pectoris) for the years 1940 through 1948 were adjusted on the basis of the above mentioned data to approximate what they would have been had the Sixth International List of Causes of Death been in use since 1940. They were thus placed

on a comparable basis with the death rates reported since 1949. These figures, shown in Fig. 1, permit us to consider the trend in the death rate from coronary artery disease—excluding arteriosclerotic heart disease so described—during the period from 1940 through 1955. Fig. 1 shows also, for the period since 1949, the trend for the broader classification of arteriosclerotic heart disease, including coronary artery disease and the component part thereof reported as arteriosclerotic heart disease.

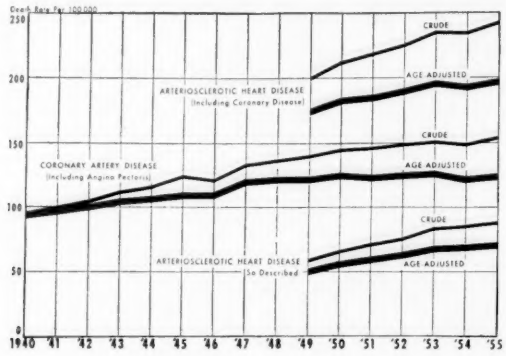

Fig. 1.—Trend of mortality from coronary artery disease (total persons, United States, 1940-1955). *Notes:* (1) Deaths classified by Sixth Revision of International List (1940-1948 estimated). (2) Age-adjusted on basis of total United States population in 1940.

The trend lines on the chart are shown in pairs, one representing the crude death rate (which is simply the ratio of the deaths for all ages combined to the corresponding population), and the other an age-adjusted death rate, which allows for changes in the age composition of the population. There has been a steady growth in the number of older persons, among whom the death rates from coronary disease are at a maximum. This trend has been an important factor in raising the crude death rate from the disease. The chart shows that the crude death rate has increased almost without interruption but that the rate of increase was much greater in the 1940's than in recent years. The age-adjusted death rate also shows a fairly steady but less rapid increase in the 1940's and in recent years it has shown little upward tendency. However, if we use the broader concept of arteriosclerotic heart disease, both the crude and the age-adjusted death rates show a moderate upward trend in recent years. Particularly noticeable is the greatly increased frequency of deaths certified as due specifically to arteriosclerotic heart disease.

There is much evidence for the conclusion that a substantial part of this increase is merely an artifact brought about by changing fashions in certifying heart disease as a cause of death. I will now discuss some of this evidence briefly.

Fig. 2 shows for the years 1940-1955 the age-adjusted death rates from coronary disease as well as from all other diseases of the cardiovascular-renal system. In contrast to an increase in the former, there was a sharp decline in the latter, with a net decline in the mortality from the cardiovascular-renal

diseases as a whole. A substantial part of the increase in the death rate from coronary disease undoubtedly represents deaths that formerly would have been reported as due to other diseases of the cardiovascular-renal system. In this connection, it is significant that in 1940, for every two deaths in which coronary artery disease was considered the primary cause, there was one more death in which it was listed as the chief contributory cause, usually with some other cardiovascular-renal disease mentioned as the primary cause. Another bit of evidence along the same lines lies in the sizable decrease (11,000) between 1940 and 1954 in the number of deaths from ill-defined causes, sudden death, and senility.

Fig. 3 compares the regional death rates from coronary disease in 1940 and 1948, both series being adjusted for geographic differences in age distribution. Clearly, the death rates have increased most rapidly in those areas where they

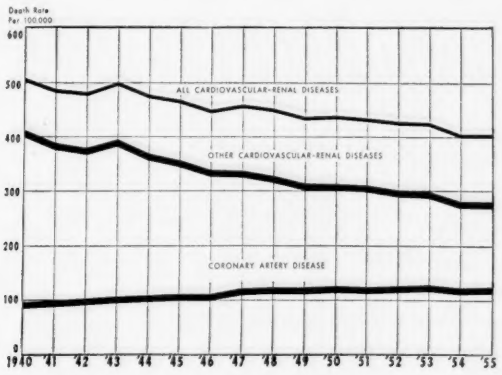

Fig. 2.—Trend of mortality from coronary artery disease and other cardiovascular-renal diseases. Age-adjusted death rates (total persons, United States, 1940-1955). *Notes:* (1) Deaths classified by Sixth Revision of International List (1940-1948 estimated). (2) Age-adjusted on basis of total United States population in 1940.

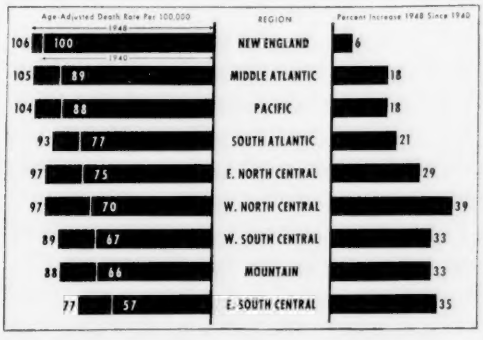
Age-Adjusted Death Rate Per 100,000
1948
1940
REGION
Percent Increase 1948 Since 1940
106 100 NEW ENGLAND 6
105 89 MIDDLE ATLANTIC 18
104 88 PACIFIC 18
93 77 SOUTH ATLANTIC 21
97 75 E. NORTH CENTRAL 29
97 70 W. NORTH CENTRAL 39
89 67 W. SOUTH CENTRAL 33
88 66 MOUNTAIN 33
77 57 E. SOUTH CENTRAL 35

Fig. 3.—Regional increases in coronary artery disease. White persons, 1940-1948. *Notes:* (1) Deaths classified by Fifth Revision of International List (Code 94). (2) Death rates age-adjusted on basis of total United States population in 1940.

were lowest in 1940. These areas were predominantly rural or had relatively few large medical centers. The most plausible explanation of these differences in trend is that the practice of certifying cases of heart disease or sudden death as coronary artery disease became common much later among physicians in the rural regions and others out of touch with large medical centers than among physicians in the highly urbanized areas. The broader concept of coronary disease and greater precision in certifying deaths undoubtedly originated in the great medical centers, then spread to urban areas generally, and were last taken up by physicians in outlying communities. Another factor was the interchange of ideas among physicians in the armed forces during World War II which accelerated the spread of the newer concepts of heart disease.

A substantial part of the increase in coronary disease and arteriosclerotic heart disease death rates reflects also more precise certification in the light of current concepts of heart disease. Thus, more and better instruction in diagnosis (including postgraduate courses in cardiology), much greater numbers of heart specialists, and greatly improved facilities for diagnosis have all served to increase the proportion of deaths ascribed to these categories of heart disease. This is brought out by the fact that the magnitude of the coronary artery disease death rates in different parts of the country is directly associated with the quantity and quality of available medical facilities. A further consideration is that the younger generation of physicians acquired the newer concepts of arteriosclerotic heart disease while in medical school, and as they replaced older physicians the frequency of coronary disease and arteriosclerotic heart disease as diagnoses on death certificates naturally increased.

The publicity given to the rise in coronary artery disease has of itself led to greater awareness of the disease. As a result, the reporting of coronary disease has apparently become fashionable with medicolegal officials. Dr. Moriyama of the National Office of Vital Statistics has recently stated[2] that it was the impression of that office that an increasing number of deaths from coronary disease were being reported by coroners and medical examiners where the deceased had not received medical attention or the cause of death was not known. In one area, more than 35 per cent of the deaths reported as coronary disease were certified by the medical examiner's office. In New York City in December, 1956,[3] some 15 per cent of the deaths from arteriosclerotic heart disease and 44 per cent of the deaths attributed to coronary artery disease were medical examiners' cases. Only a very small proportion (4 per cent and 8 per cent, respectively) of these diagnoses were verified by autopsy, in contrast to a very much higher proportion (40 per cent) of patients autopsied for other causes. Of the nonhospital deaths in New York City ascribed to coronary disease, no less than 57 per cent were certified by medical examiners, but in only about 5 per cent of such cases was an autopsy performed. The proportion of autopsies was even smaller in nonhospital cases ascribed to arteriosclerotic heart disease. Even in the less sizable group of deaths from arteriosclerotic heart disease and coronary disease occurring in hospitals in which the certification was made by the medical examiner, the percentage of autopsies was far lower than for all other causes combined (Table I).

TABLE I. PROPORTION OF DEATHS FROM ARTERIOSCLEROTIC HEART DISEASE AND ALL OTHER CAUSES CERTIFIED BY MEDICAL EXAMINERS AND BY PRIVATE PHYSICIANS IN WHICH AN AUTOPSY WAS PERFORMED
(New York City deaths, December, 1956)

CAUSE OF DEATH	PER CENT CERTIFIED BY MEDICAL EXAMINER	PER CENT OF DEATHS AUTOPSIED			NUMBER OF DEATHS		
		TOTAL	DEATHS CERTIFIED BY:		TOTAL	CERTIFIED BY:	
			MEDICAL EXAMINER	PRIVATE PHYSICIAN		MEDICAL EXAMINER	PRIVATE PHYSICIAN
	All Deaths						
Arteriosclerotic heart disease, total	28.5	7.6	6.6	8.0	2,505	713	1,792
So described	14.6	7.1	3.6	7.7	1,325	194	1,131
Coronary artery disease	44.0	8.2	7.7	8.6	1,180	519	661
All other causes*	20.3	25.7	39.6	22.2	4,697	955	3,742
	Deaths in Hospital						
Arteriosclerotic heart disease, total	12.6	12.8	15.1	12.5	1,322	166	1,156
So described	6.0	10.7	7.8†	10.8	853	51	802
Coronary artery disease	24.5	16.6	18.3	16.1	469	115	354
All other causes*	14.4	29.6	44.0	27.2	3,558	514	3,044
	Nonhospital Deaths						
Arteriosclerotic heart disease, total	46.2	1.9	4.0	—	1,183	547	636
So described	30.3	0.6†	2.1†	—	472	143	329
Coronary artery disease	56.8	2.7	4.7	—	711	404	307
All other causes*	38.7	13.6	34.5	0.4†	1,139	441	698

Note: No deaths were ascribed to angina pectoris.
*Includes violent and accidental deaths.
†Based upon less than 5 autopsies.

To sum up, about 30 per cent of the increase from 1940 to 1955 in the crude death rate from coronary disease can be accounted for by the greater proportion of persons at the older ages. Another 40 per cent of the increase in the crude death rate can be ascribed directly to the changes in procedures and classification adopted in 1949 with the Sixth Revision of the International List of Causes of Death. In my judgment, a major part of the remaining 30 per cent represents merely the acceptance of a broader concept of coronary disease, better diagnoses, and increasing usage of the term coronary artery disease in certifying causes of death. In other words, probably less than 15 per cent of the increase in the death rate can be attributed to a real increase in the mortality from this disease.

TREND OF DEATH RATE BY SEX

The foregoing estimate of the weights of the several factors responsible for the increase in the number of coronary disease deaths in the entire population obscures the different trends in the mortality from this disease by sex. Fig. 4 presents the trends of mortality from coronary disease for white males and for white females. It shows that over the 15-year period since 1940, the age-adjusted death rate from the disease increased about 40 per cent for males but only about 15 per cent for females; in fact, since 1947 there has been little change in the coronary disease death rate of white females.

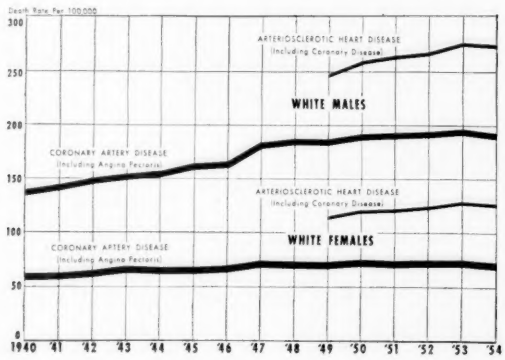

Fig. 4.—Trend of mortality from coronary artery disease by sex. Age-adjusted death rates. (United States, 1940-1954.) *Notes:* (1) Deaths classified by Sixth Revision of International List (1940-1948 estimated). (2) Age-adjusted on basis of total United States population in 1940.

Among white males the increase in death rates was fairly uniform by age, but among white females it was concentrated at the ages of 45 and over.

On the basis of the broader concept of arteriosclerotic heart disease, there has been a 10 per cent increase in the age-adjusted death rates for both white males and white females since 1949. However, this has been more than outweighed by the decline in the death rate from other cardiovascular-renal diseases.

The fact that the increase in coronary disease death rates since 1940 has been so much more pronounced for white males than for white females argues that some part of the rise among white males is real, since a change in the terminology of reporting heart disease on death certificates is not likely to have affected males so much more than females. On the other hand, the relatively small increase in the age-adjusted death rates from coronary disease among white females can probably all be accounted for by the acceptance of a broader concept of this disease and increasing usage of the term coronary artery disease.

SEX DIFFERENTIALS

Fig. 5 shows the current (1954) sex differentials in mortality from arteriosclerotic heart disease among white persons in the general population. It also

indicates that arteriosclerotic heart disease is concentrated largely among males over 45 years and females over the age of 55.

At the ages of 35 to 44, white male death rates are approximately 6.6 times those for females; at ages 45 to 54 the differential declines to 5.3 times and then decreases progressively with advance in age to only 1.4 times at the ages of 75 to 84. At ages 85 and over the death rates for the two sexes are about equal.

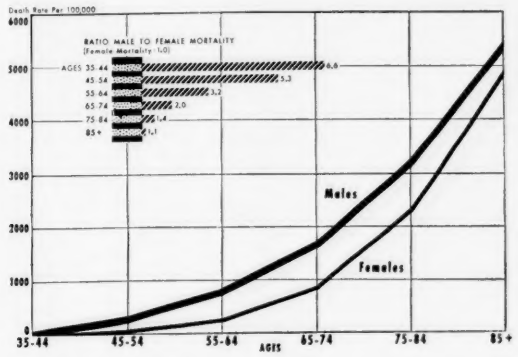

Fig. 5.—Arteriosclerotic heart disease by age and sex. White persons, United States, 1954. Includes coronary artery disease.

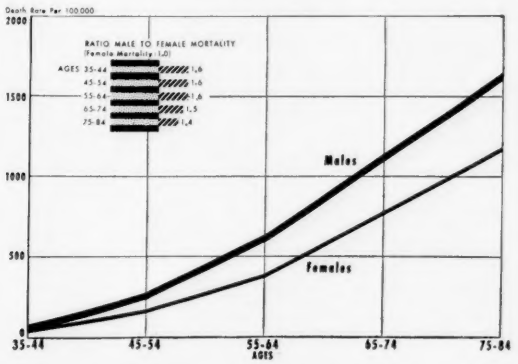

Fig. 6.—Arteriosclerotic heart disease by age and sex. Nonwhite persons, United States, 1954. Includes coronary artery disease.

Fig. 6 shows the 1954 death rates from arteriosclerotic heart disease among nonwhite persons in the general population and brings out that the death rates of nonwhite males average only about 1½ times that for nonwhite females. As Fig. 6 indicates, the sex ratio varies comparatively little with age. It is 1.6 in the age range from 35 to 64 and decreases to 1.4 at the ages of 75 to 84.

In England, Canada, and Australia, the sex differentials in arteriosclerotic heart disease are quite similar to those among white persons in the United States. In Italy and Portugal, they are very much lower, being more nearly of the order of 1½ times, or about the same as among nonwhites in the United States. This indicates that under some circumstances the influence of sex on the incidence

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of arteriosclerotic heart disease is much smaller than that observed among white persons in the United States.

The sex differential in mortality from arteriosclerotic heart disease at ages under 55 is greater than that for any other demographic factor. Any theory as to the etiology of arteriosclerotic heart disease should account for the sex differentials in the mortality from this disease as between various countries and as between white and nonwhite persons in the United States.

RACE DIFFERENTIALS

The death rates from arteriosclerotic heart disease of white and nonwhite males are not markedly different at the ages under 45 years. At the ages of 45 and over, the recorded mortality rates of nonwhite males fall increasingly below those of white males with advance in age. However, the reporting of deaths among older nonwhites is known to be deficient, both as to numbers and cause, and a high proportion of the elderly nonwhite population lives in regions from which relatively low death rates from arteriosclerotic heart disease are being reported even for whites. If allowance were made for these factors, the death rates from this disease among older nonwhite males would undoubtedly be closer to those of white males.

In sharp contrast to the situation among males, arteriosclerotic heart disease mortality rates of nonwhite females are 4 times those of white females at the ages of 35 to 44 and more than 2½ times at the ages of 45 to 54. Even at ages 55 to 64, nonwhite females are subject to 1½ times the death rate of white females. However, at ages 65 and over, the recorded death rates of nonwhite females are lower than those of white females. Again this may primarily reflect underreporting of deaths among elderly nonwhite females as well as their geographic distribution.

The high death rates among nonwhite females, especially at the younger ages, suggest either that some special factors operate in the development of arteriosclerotic disease among them or that other types of heart disease are being certified erroneously as arteriosclerotic heart disease in this segment of the population.

The death rates from coronary disease have during the past 15 years increased much faster among nonwhites than among white persons. Much of this may reflect the increasing exposure of the nonwhite population to modern medicine, as a result of large scale migration from the rural South to northern cities. Particularly significant in this connection is the fact that between 1940 and 1954, the age-adjusted death rate from coronary artery disease increased by over 70 per cent for nonwhite males compared with only about 40 per cent for white males, and that the largest increases in coronary artery disease death rates among nonwhite males occurred at the ages of 55 to 74 (in excess of 100 per cent). In like manner, the age-adjusted death rates of nonwhite females have increased very much more than for white females, especially at the ages of 55 and over.

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VARIATIONS BY MARITAL STATUS

Analyses of mortality statistics according to marital status have repeatedly brought out that death rates are lowest among the married and highest among the divorced and the widowed, with death rates among the single only somewhat below those among the divorced and the widowed. These mortality differentials have been attributed to factors associated with marriage. An analysis of the 1940 death rates by cause showed markedly higher mortality from the heart diseases as a group among the single, widowed, and divorced (in that order) than among the married. A more recent analysis made in the Public Health Service of the 1950 death rates by cause[4] indicated (Table II) that among white men at ages 45 to 74 years the death rate from arteriosclerotic heart disease was about 25 per cent higher for the widowed than for the married and about 35 per cent higher for the single and the divorced combined. Among white females the excess mortality for the widowed was about the same as among males, but the death rate among the single and divorced was only about 10 per cent higher than among the married. The differentials in mortality from arteriosclerotic heart disease by marital status are considerably greater at ages under 45 years. It would appear, therefore, that factors associated with marital status, mainly, the biologic selectivity of marriage and the more favorable environment of the married, have a definite influence on the level of mortality from arteriosclerotic heart disease.

TABLE II. VARIATIONS IN ARTERIOSCLEROTIC HEART DISEASE MORTALITY BY MARITAL STATUS
(White persons at ages 45 to 74—United States 1949-1951)

	DEATH RATE PER 100,000	PER CENT OF RATE FOR MARRIED
White Males		
Married	690	100
Widowed	838	122
Single and divorced	922	134
White Females		
Married	221	100
Widowed	274	124
Single and divorced	239	108

Includes coronary artery disease.

GEOGRAPHIC VARIATIONS

A recent study made by the Public Health Service[5] of the geographic variation in the death rates from arteriosclerotic heart disease recorded in 1950 concluded that the differences in mortality in different parts of the country represented for the most part real differences in the incidence of this disease. This conclusion was necessarily qualified because some of the geographic variation in death rates undoubtedly reflected differences in practices of certifying causes of death and differences in medical standards.

Fig. 7 shows the age-adjusted death rates from arteriosclerotic heart disease for white males by state. In 1950, the highest death rates were recorded in the Middle Atlantic states and New England and the lowest in the East South Central states followed by the West South Central and the Mountain states. The same pattern was observed for white females. The individual states with the highest death rates for white males were New York, Rhode Island, District of Columbia, California, Connecticut, New Hampshire, and Massachusetts (all in excess of 335 per 100,000); the lowest death rates prevailed in New Mexico, Arkansas, Kentucky, and Tennessee (all below 220 per 100,000). The death rate in New York was about double that in New Mexico for both white males and white females.

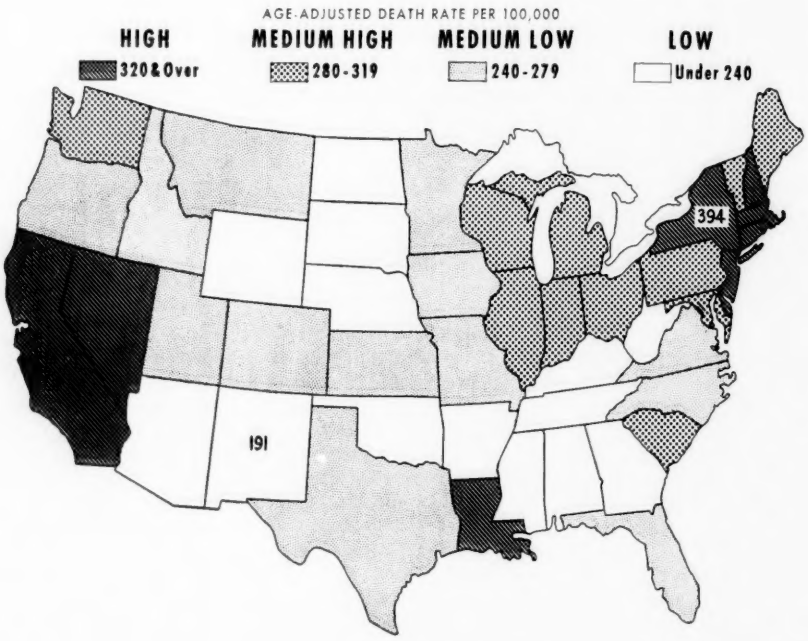

Fig. 7.—Geographic variations in arteriosclerotic heart disease. White males, 1950 *Notes*: (1) Includes coronary artery disease. (2) Age-adjusted on basis of total United States population in 1950.

Broadly speaking, the highly urbanized states or those with or close to large medical centers had high rates, while the predominantly agricultural states recorded low rates. The unexpectedly high death rates in Nevada and Delaware (over 330 per 100,000) may reflect in part the influence of the medical standards in adjoining states; the almost equally high death rate in Louisiana may similarly derive from the influence of the medical faculties in New Orleans which have made that city one of the outstanding medical centers in the country.

The Public Health Service study[5] which produced these figures brought forward evidence of wide differences in the terminology used in certifying deaths at the older ages. Such differences are responsible for part of the recorded mortality differential between the regions with the highest and the lowest death rates.

Nevertheless, the study concluded that the major part of the differences in death rates represented real geographic differences in the incidence of the disease. To some extent, this is certainly true, but in my judgment, the effect of regional differences in the certification of causes of death from degenerative conditions should be given greater weight. My opinion in this respect is supported by the different but complementary pattern of mortality from other cardiovascular-renal diseases and also by the high positive correlation between the number of internists (including cardiologists) per 100,000 population and the level of the death rate from arteriosclerotic heart disease (Table III).

TABLE III. CORRELATION BETWEEN MORTALITY FROM ARTERIOSCLEROTIC HEART DISEASE AND INTERNISTS PER 100,000 WHITE PERSONS
(United States, 1950)

REGION	AGE-ADJUSTED DEATH RATE PER 100,000	NUMBER OF INTERNISTS* PER 100,000
Middle Atlantic	273	12.6
New England	250	10.5
Pacific Coast	233	9.7
East North Central	214	7.3
South Atlantic†	193	7.6
West North Central	183	6.7
Mountain	179	6.5
West South Central	176	5.8
East South Central	160	4.5

Includes coronary artery disease. Death rates age-adjusted on basis of total U. S. population in 1950.

*Includes cardiologists.

†Excludes District of Columbia.

Of interest also is a comparison of the death rates from arteriosclerotic heart disease in New York City and the rest of New York State. For males, the New York City death rates in 1953 were slightly lower than in the rest of the state at ages under 45 years but markedly higher at ages 45 and over. For females, the New York City death rates were slightly lower than those upstate only in the age range under 35 but were markedly higher at the ages of 45 and over (Table IV).

VARIATIONS BY SOCIOECONOMIC STATUS

Some light on the differences in arteriosclerotic heart disease death rates according to socioeconomic status can be obtained from the mortality experience among different classes of insured lives, notably "industrial" and "ordinary" policyholders.

Industrial policyholders are for the most part members of urban wage-earning families in the lower income brackets. They include a high proportion of men engaged in manufacturing and mechanical industries, in mining, in transportation, and in personal service. Ordinary policyholders are drawn mainly from the urban middle and well-to-do classes of the population engaged in non-hazardous occupations, such as the professions, business, trade, and clerical occupations.

TABLE IV. DEATH RATES FROM ARTERIOSCLEROTIC HEART DISEASE NEW YORK CITY AND REST OF NEW YORK STATE

(By Sex and Age—1953)

AGE GROUP	DEATH RATE PER 100,000	
	NEW YORK CITY	REST OF NEW YORK STATE
Males		
All ages	455.9	399.3
Under 25 years	0.5	0.1
25-34 years	9.7	12.2
35-44 years	87.1	87.4
45-54 years	400.2	352.5
55-64 years	1,128.6	971.3
65-74 years	2,392.8	1,947.0
75 years and over	5,603.2	4,475.2
Females		
All ages	285.1	244.9
Under 25 years	0.1	0.2
25-34 years	1.8	2.0
35-44 years	15.7	14.2
45-54 years	106.7	76.4
55-64 years	465.9	348.0
65-74 years	1,469.0	1,067.8
75 years and over	4,770.1	3,418.8

Includes coronary artery disease.

TABLE V. ARTERIOSCLEROTIC HEART DISEASE DEATH RATES AMONG ORDINARY AND INDUSTRIAL POLICYHOLDERS

(White Males Insured in Metropolitan Life Insurance Company—Experience in 1953)

AGE GROUP	DEATH RATE PER 100,000	
	ORDINARY POLICYHOLDERS	INDUSTRIAL POLICYHOLDERS
35–44	73.8	98.1
45–54	342.1	375.7
55–64	907.8	917.8
65–74	1,961.1	1,842.1
75–84	3,917.8	

Includes coronary artery disease.

A comparison between the 1953 death rates from arteriosclerotic heart disease among industrial and ordinary policyholders of the Metropolitan Life Insurance Company (Table V) reveals an inverse relationship between mortality and socioeconomic status at ages under 65 years. At these ages white male industrial policyholders, who by and large represent the lower socioeconomic groups, experienced distinctly higher death rates from arteriosclerotic heart disease than

white ordinary policyholders, who on the whole represent the more favored socioeconomic groups. These trends are corroborated by a recent Public Health Service study of heart disease in Baltimore[6] which also indicated that at ages under 65 years the lowest death rates from arteriosclerotic heart disease were in the highest socioeconomic groups.

These findings are contrary to what would have been expected from other considerations such as quality of medical care, social and occupational stresses, and diet since it is in the higher socioeconomic groups that we should find better diagnoses, greater social and occupational stresses, and richer diet. It is noteworthy that among males in England and Wales the highest death rates from coronary disease are found in the highest socioeconomic class,[7] but among married women in England and Wales the mortality from coronary disease increases as as we go from the highest to the lowest socioeconomic groups, determined on the basis of the husband's occupation.

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SOME SPECIAL FACTORS ASSOCIATED WITH CORONARY ARTERY DISEASE

Mortality investigations of insured lives, which study the effect of various physical characteristics, shed light on some other factors assiocated with an increased death rate from coronary artery disease.

TABLE VI. MORTALITY AMONG INSURED OVERWEIGHTS
(Metropolitan Life Insurance Company, 1925-1950.)

	RATIO OF ACTUAL DEATH RATE TO THAT AMONG STANDARD RISKS	
	ALL CAUSES (PER CENT)	HEART DISEASE (PER CENT)
White Males		
Standard* weight range	100	100
Moderately overweight	142	146
Markedly overweight	166	167
White Females		
Standard* weight range	100	100
Moderately overweight	142	145
Markedly overweight	155	174

*Accepted for insurance at standard premium rates; includes some slightly overweight.

Thus, a long series of studies of insured lives with respect to body build, dating back to the beginning of the century, have consistently shown that individuals who are overweight experience a markedly higher mortality than persons of about average weight, and that this excess mortality is primarily due to cardiovascular diseases. A study made several years ago in the Metropolitan Life Insurance Company[8] of some 50,000 men and women who were charged extra premiums because of overweight and who were followed for periods up to 25 years, showed 40 per cent higher total mortality than normal for those moderately overweight and 65 per cent higher mortality for those markedly overweight (Table VI). The bulk of this excess mortality was due to cardiovascular-

renal diseases, primarily of arteriosclerotic origin. This study also showed that persons who had reduced their weight sufficiently to be eligible for standard insurance experienced virtually normal mortality. The first fragmentary returns from the Framingham Heart Epidemiology study confirm the adverse effect of overweight on the incidence of arteriosclerotic heart disease.[9]

A more recent study made in the Metropolitan Life Insurance Company of insured lives who were not only moderately overweight but also had a slight elevation in blood pressure disclosed very high mortality from heart disease among them (about 130 per cent higher than among standard risks) with arteriosclerotic heart disease being responsible for most of the excess mortality. Mortality from heart disease was even higher among those moderately overweight with a moderate elevation in blood pressure. The initial findings in the Framingham study likewise indicate that the combination of overweight and hypertension has a greater adverse effect on the incidence of arteriosclerotic heart disease than either factor alone.[9]

There is currently in progress a comprehensive intercompany investigation of mortality among insured lives according to variations in build and blood pressure which is expected to furnish more definite evidence as to the relationship between overweight, elevated blood pressure (as well as combinations of these impairments), and the mortality from coronary artery disease.

TABLE VII. MORTALITY AMONG INSURED PERSONS REPORTING TWO OR MORE CASES OF EARLY CARDIOVASCULAR-RENAL DISEASE IN THEIR FAMILIES

(Experience of 27 companies on about 18,000 lives, 1935-1950)

	RATIO OF ACTUAL MORTALITY TO THAT AMONG STANDARD RISKS (PER CENT)		
	ALL CAUSES	HEART AND CIRCULATORY DISEASES	CORONARY HEART DISEASE
Persons insured at standard premium rates			
No record of impairment	141	175	180
With minor impairments*	170	about 250	
Persons insured at substandard rates, largely with minor impairments	185	256	

*Based on the experience of two companies only.

A recent intercompany investigation of insured lives,[10] comprising a follow-up of nearly 18,000 persons for periods up to 15 years, showed conclusively that persons who had reported two or more cases of early cardiovascular-renal disease in their families were themselves subject to death rates from cardiovascular disease which were from 1¾ to 2½ times those prevailing among standard risks (Table VII). Among persons who in addition to a family history of two or more cases of early cardiovascular-renal disease reported minor impairments of the cardiovascular system, such as moderate overweight or a slight elevation in blood pressure, the excess mortality from cardiovascular disease was even higher. This, together with similar findings of earlier studies[11] as to the effect on mortality

of a family history of cardiovascular-renal disease strongly suggests that a constitutional or hereditary factor has considerable influence on the level of mortality from coronary artery disease.

A number of investigators have reported a high degree of association between death rates from heart disease and cigarette smoking. Hammond and Horn[12] found that, in the United States among white males in the age group of 50 to 54, the coronary disease death rate among those smoking a pack or more cigarettes a day was nearly 2½ times as high as the rate for nonsmokers. This association tended to diminish with advancing age and virtually disappeared at ages over 65 years. Doll and Hill[13] in England found a smaller but nevertheless significant association with smoking which was distinct only at ages under 55. Of course, even a high degree of statistical association does not necessarily imply that excessive cigarette smoking is a cause of coronary disease. As the scientific director of the Tobacco Research Committee has pointed out, "Scientists generally agree that statistical associations alone do not provide proof of cause and effect."[14] The effect of smoking on existing coronary disease remains to be appraised authoritatively.

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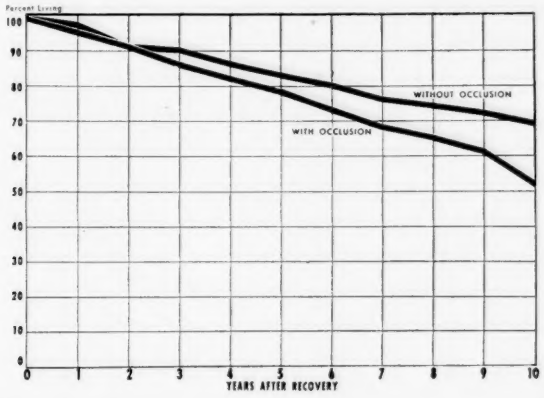

Fig. 8.—Survivorship after recovery from disability due to arteriosclerotic heart disease. White males, Metropolitan Life Insurance Company, 1925-1952. Cases insured under standard ordinary policies in which disability terminated by recovery in 1925-1949. In 420 cases, there was a history of occlusion and in 117 no history of occlusion. (These men were not impaired when insurance was issued.)

SURVIVORSHIP AFTER RECOVERY FROM DISABILITY FROM CORONARY DISEASE

From the records of insured lives who were granted disability benefits in connection with ordinary life insurance policies, it has been possible to study the longevity of persons who were totally and permanently disabled by coronary disease for a period of at least three months and subsequently recovered sufficiently to be able to resume work. Persons who died soon after an attack or who were not disabled for a period of at least three months were not included in the study.

The results of such a study made several years ago in the Metropolitan Life Insurance Company[15] are presented in Fig. 8; this shows the proportion surviving

on successive anniversaries after recovery for persons in the age range from 30 to 70 years who recovered from disability due to arteriosclerotic heart disease. The total number of such cases traced was 537, of whom 420 had a history of occlusion. It was found that the proportion surviving ten years after recovery was 70 per cent in cases without occlusion and 53 per cent in cases with occlusion. The mortality rates among such selected cases without occlusion were about 2½ times those among standard insured risks, while the death rates on cases with occlusion were about 4 times those among standard risks.

While it would be of great interest to determine the average length of life of persons disabled by coronary disease as well as for those who recovered from an acute occlusion, any such determination would have to be based partly on assumptions as to the mortality rate subsequent to the period of actual observation. It is for this reason that statements as to the longevity of persons who recovered from coronary disease have been confined to the actual experience during the period of observation.

CONCLUSION

For a variety of reasons which I have indicated, it is difficult to evaluate the real trend of mortality from coronary disease. The best that can be done from available mortality records is to make judicious estimates and to note where gross biases probably exist. This difficulty will remain until there is more uniformity in the description of specific types of heart disease on death certificates. Nevertheless, available evidence points only to a modest increase in the mortality of white males over the last fifteen years (probably less than a fifth of the recorded increase being real) and little, if any, increase in the mortality among white females. Moreover, the data furnish considerable evidence that a number of seemingly unrelated factors are implicated in the increased death rate from coronary disease among white males. It is important to guard against the tendency to oversimplify and overgeneralize in accounting for the variations in the incidence of the disease in different groups, at different times, and in different places. The notion of a single cause, so useful in considering the etiology of acute communicable diseases, has not been fruitful in dealing with chronic diseases. I believe it would be more profitable if, in our thinking with respect to all chronic diseases and with respect to arteriosclerotic heart disease in particular, we recognized that a hypothesis of multiple causation appears to be more consistent with the known facts.

Fortunately, in the extensive research being conducted in the field of cardiovascular disease, recognition has been given to numerous factors that bear on the etiology and development of these conditions. The growing importance of these diseases as causes of morbidity and mortality, and the consequent need for investigation of measures to control them are spurring increasing research activities. As early as 1945, the life insurance business established the Life Insurance Medical Research Fund which has concentrated on research on cardiovascular diseases. In the 11 years since it began to function the Fund has spent or appropriated more than $8,000,000 for this purpose. Currently, the outlays of the Fund for research amount to approximately $1,000,000 a year, which ranks the Fund as one of the major sources of support for such research.

There is good reason to be optimistic about the eventual results of the extensive research on cardiovascular diseases, although the factors involved are so many and so complex that progress may be slow. Even with our present knowledge, however, the chances of functional recovery from coronary attacks and of reasonably good longevity thereafter are much better than many laymen realize.

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SOME EPIDEMIOLOGIC ASPECTS OF CORONARY ARTERY DISEASE

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THE primary public health problem of our country and of many other well-developed areas in the world is cardiovascular disease, particularly of middle-aged men. Coronary artery disease represents a large share of this group of disabling and killing diseases.

The Third Regional World Health Organization Conference of Europe, meeting in Copenhagen in 1953, recognized cardiovascular disease as a public health problem of international concern and recommended that a study group be set up to stimulate action in this field. In 1954, the Food and Agriculture Organization and the WHO Expert Committee on Nutrition proposed that WHO give consideration to the relation of diet and the development of atherosclerosis. The first study group on atherosclerosis and ischemic heart disease met in Geneva in November, 1955, and included representatives from many scientific disciplines.[1]

Diseases of the coronary arteries involve two main pathologic processes, atherosclerosis or thrombosis of one or more branches, occurring alone or in combination. Atherosclerosis of the arteries may include several of the following conditions: fat deposits and fibrous thickening of the intima, principally, plus hemorrhage, calcification, or tissue necrosis. The same processes may be responsible for cerebral or peripheral vascular disease and may be concurrent in an individual with coronary artery disease. The end product of coronary artery disease, myocardial damage, is a major public health problem because of the illness, disability, or death that inevitably follow in its wake. Coronary artery disease may be present with or without evidence of myocardial damage, in persons of all ages; it has been found in young soldiers killed in battle and in post-mortem examinations of a high proportion of persons dying from causes other than cardiovascular.

In coronary artery disease, it would appear that we are dealing with a disease entity that has multiple factors in its causation and its manifestations as well. By observing its natural history among people under varying environmental conditions and modes of life, we can hope to unmask some of its hidden secrets. This is the epidemiologic method of study. Even though we do not know the cause of coronary artery disease, we can still obtain a considerable measure of

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control if we can learn enough about its epidemiologic characteristics to detect its occurrence early and prevent its progression.

DIAGNOSTIC CRITERIA

The first requirement for studying coronary artery disease in a population group is a definition of the term itself. Diagnostic criteria in both the living and the dead are necessary, because the disease does not manifest itself in the living unless myocardial damage is sufficient to cause clinical signs and symptoms.

A practical epidemiologic definition of the disease is atherosclerosis, thrombosis, or embolism, singly or in combination, of the coronary arteries sufficient to produce clinical evidence of myocardial damage in the living individual, either at rest or under various types of stress. In the dead, this disease entity can be more precisely described from post-mortem examination, but one can not always determine whether the atherosclerosis or the thrombosis—with organization of the clot—came first.

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In the living, coronary artery disease may be diagnosed by history, physical or laboratory examinations, including stress tests, in a variety of combinations. Between the two extremes, one, a history alone of angina pectoris and, the other, a classical picture of a positive history, physical and laboratory findings of myocardial infarction, is an indeterminate group of findings that can be classified as coronary artery disease. Unless the observer specifies his diagnostic criteria and subdivides his study population accordingly, his results are of little comparative value in helping us to understand coronary artery disease.

A variety of diagnostic categories is also found on post-mortem examination. The number, location, and size of atheromatous plaques, the degree and location of arterial narrowing, the size, shape, and position of thrombi, ulcers, and calcifications are given different interpretations by different pathologists. Comparisons of post-mortem findings without uniform diagnostic criteria are difficult to interpret; unfortunately, at present there is no national or international standard nomenclature for such findings in coronary artery disease.

Accuracy and completeness of certificates of death vary from state to state and country to country, and also from time to time as nomenclatures are modified and amended. The last important changes were made in 1949, so we must be careful in making comparisons before and after that date. Vital statistics, even in the United States, have limitations when used for comparative purposes, especially when categories of disease are used, instead of deaths from all causes.

VITAL STATISTICS

The great biostatistician, Raymond Pearl, always questioned the possibility of expressing a complex of morbid conditions in terms of a single cause, such as heart disease. He limited conditions acceptable under a heading of a single cause to deaths from all causes and to accidental deaths. DePorte,[2] quoting Pearl's views, pointed out that we are forced, in the practical conduct of statistical work in health departments, to deal with other headings than deaths from all causes; but in so doing, one should always remember that this material is fundamentally of a dubious character. Moriyama[3] of the National Office of Vital Statistics concluded in a paper published in April, 1956, on the "Develop-

ment and Present Concept of Cause of Death" that "the traditional compilation of statistics on causes of deaths have proved of value in the past when public health was chiefly concerned with infectious diseases. With the increase in public health importance of the chronic diseases there is a growing indication of inadequacy in the statistics now being compiled."

So one must interpret with many reservations statistical studies comparing mortality rates for heart disease with such factors as levels of fat consumption, especially from one country to another. Parallel trends can be shown to furnish interesting clues, as Keys[4] has so ably done, but these findings cannot be accepted as cause and effect relationships between certain nutrients and coronary artery disease.

The following excerpt from the Report of the Ministry of Health of Great Britain for 1954[5] is to the point: "Like fat intake, deaths from arteriosclerotic heart disease show postwar increases. It is noteworthy, however, that when prewar death rates and fat consumption levels are related, this association breaks down, fat consumption levels being high, whereas arteriosclerotic heart deaths were less than half what they are today."

As an example of this epidemiologic principle, one of the members of our 1955 study group in Geneva, Yerushalmy,[6] Professor of Biostatistics at the University of California School of Public Health, assembled data from WHO sources[1] on the possible association between per cent of calories from fat in the national diet and cardiovascular diseases. Yerushalmy has kindly permitted me to use his unpublished material. Data on fat consumption, cardiovascular deaths,

TABLE I. MORTALITY IN 12 COUNTRIES FROM HEART DISEASE FOR MALES AND PER CENT OF CALORIES DERIVED FROM FAT

COUNTRIES	RATES PER 100,000 BY AGE							PER CENT OF CALORIES FROM FAT
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	
Australia	90.6	203.7	387.4	705.7	1161.9	1832.1	2750.9	33
Canada	121.8	238.6	424.2	711.2	1095.4	1555.6	2335.5	40
German Federal Republic	61.1	117.8	245.4	308.7	504.4	773.8	1307.6	35
Denmark	42.0	105.8	209.8	377.0	632.0	1011.6	1819.9	39
Israel	69.5	146.0	284.1	423.7	850.0	1125.4	1660.2	23
Italy	56.6	107.1	192.3	312.4	512.7	860.9	1518.2	21
Japan	46.7	73.6	113.9	190.2	303.8	512.2	713.1	8
Netherlands	36.8	72.5	156.4	253.7	454.4	780.8	1366.1	37
New Zealand	80.4	195.4	356.3	624.3	1084.4	1675.9	2536.7	40
Portugal	55.6	97.9	164.6	274.2	482.2	870.4	1432.1	25
Sweden	41.8	103.3	190.3	364.8	621.0	1050.8	1657.0	39
United States	159.1	308.1	542.6	883.9	1312.4	1931.2	2781.8	39

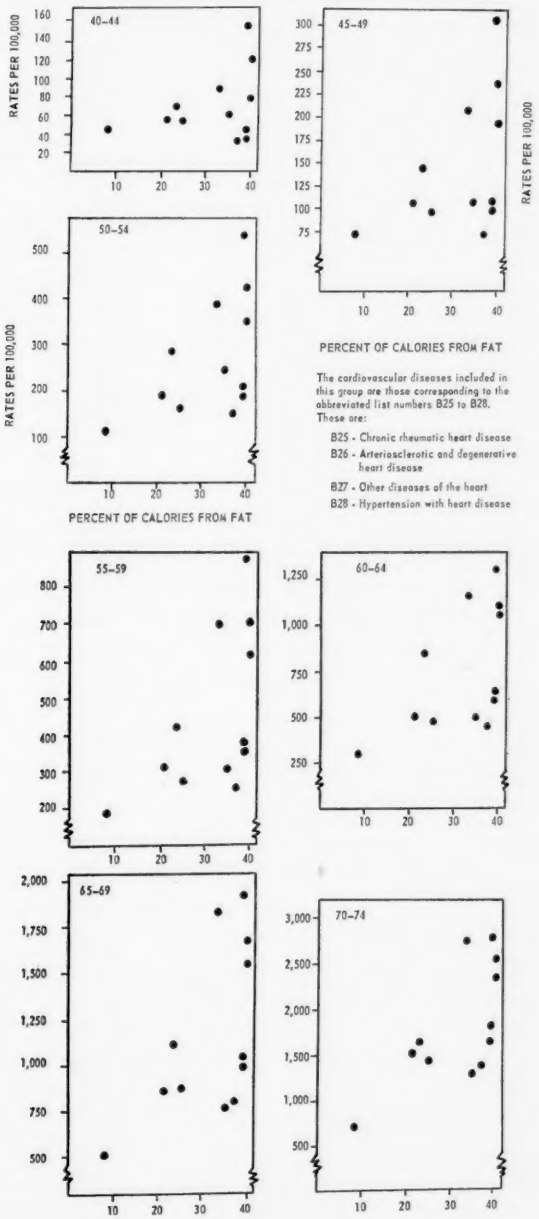
All countries for which the dietary source of calories are given in Working Paper No. 6 of the WHO Study Group on Atherosclerosis and for which deaths from these diseases and recent population estimates are available were utilized. Deaths and population estimates are for the three-year period 1950-1952.

The cardiovascular diseases included in this group are those corresponding to the abbreviated list numbers B 25 to B 28.

These are: B 25—Chronic rheumatic heart disease; B 26—Arteriosclerotic and degenerative heart disease; B 27—Other diseases of the heart; B 28—Hypertension with heart disease.

Source of mortality and population data: WHO, Annual Epidemiological and Vital Statistics, 1950-1952; Working Paper No. 9, WHO Study Group on Atherosclerosis.

and population estimates were available from 12 countries—Australia, Canada, German Federated Republics, Denmark, Israel, Italy, Japan, Netherlands, New Zealand, Portugal, Sweden, and the United States (Table I). Scatter diagrams (Fig. 1) were made for males for each of seven age groups by per cent of calories


40–44
45–49
50–54
55–59
60–64
65–69
70–74
RATES PER 100,000
PERCENT OF CALORIES FROM FAT
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B25 - Chronic rheumatic heart disease
B26 - Arteriosclerotic and degenerative heart disease
B27 - Other diseases of the heart
B28 - Hypertension with heart disease

Fig. 1.—Scatter diagrams of 12 countries according to per cent of calories derived from fat and mortality from heart disease for males, by age.

derived from fat and by death rates per 100,000 persons from heart disease classified under items B25 to B28 of the International List of Causes of Death. It is apparent from these scatter diagrams that there is no sound basis for the statement that a strong parallelism in the different countries exists between fat consumption and heart disease mortality. In countries where the calories derived from fat were between 30 and 40 per cent, there were extreme variations in the cardiac death rates, in each of the seven age groups shown.

Yerushalmy also prepared scatter diagrams for the same countries relating the per cent of calories from animal protein to deaths from heart disease, using the same classifications by age and death rates (Fig. 2). A comparison of the scatter diagrams of Figs. 1 and 2 shows that the association of heart disease mortality is obviously greater with consumption of animal protein than with fat.

Yerushalmy pointed out that there is no intention to suggest that animal protein consumption is related to mortality from heart disease but merely that the above methods of attempting to demonstrate causal relationships between food consumption and heart death rates are inadequate. The lack of association in Fig. 1 does not imply that there is no relationship between fat consumption and heart disease, but it does indicate that one should interpret with caution such results from the 12 countries listed.

It is encouraging that in this country, there is a movement to obtain morbidity statistics on a large scale, in addition to mortality data. In October, 1956, the United States Public Health Service established a National Health Survey Program to conduct a continuing survey of the United States population to determine the extent of illness and disability by age, sex, and occupation, plus social and economic factors.[7] This survey will consist of repeated household interviews of representative samples of the population plus clinical examinations of subsamples of the interviewed members. Although there are known limitations to questionnaire-type surveys, we should be able to obtain new information on the relationship between nutrients and other factors and coronary artery disease.

CONSTITUTIONAL FACTORS

In coronary artery disease, as in other diseases of unknown etiology, it is not easy to dissociate hereditary from environmental factors. This is especially true in attempting comparisons of coronary artery disease morbidity and mortality among different populations living under varying conditions throughout the world. Observed differences in selected samples of these populations are open to question on at least two counts; first, the samples may not be representative of the two populations; and second, the genetic factors and the variations in modes of life are not always differentiated in the studies.

Study of somatic types and coronary artery disease has not revealed any significant clues. The same is true of psychosomatic types. Gertler and White[8] found coronary artery disease in all body types but in their sample, 44 per cent were in the mesomorphs.

In countries such as the United States, Great Britain, and Sweden, men in the age groups 30 to 50 years show much higher mortality rates from coronary artery disease than females. Yet in the Netherlands, until recently, this has

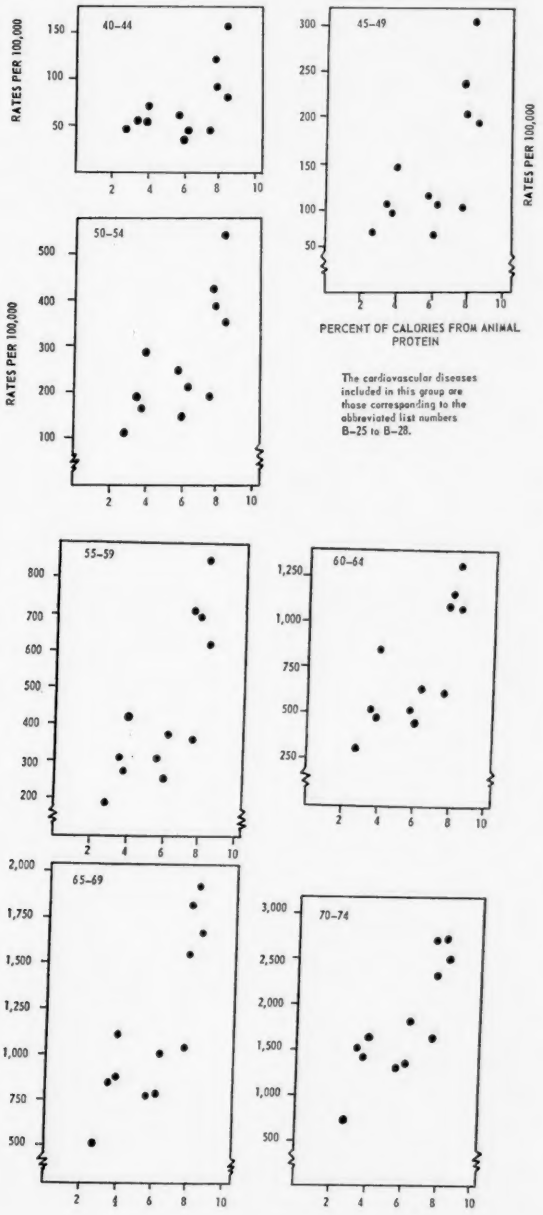

Fig. 2.—Scatter diagrams of 12 countries according to per cent of calories derived from animal protein and mortality from heart diseases, by age.

not been so. The interpretation of sex differences in coronary artery disease mortality is difficult to make, and yet these characteristics require consideration in any epidemiologic study. Men and women live differently in many ways and have diverse sex-linked characteristics, both genetic and environmental. DePorte,[9] who has been studying the vital statistics of marriage and survival for many years, found that in the United States for the period 1949-1951 the risk of deaths from coronary artery disease is greater among divorced than among married women at all ages, but this is also true of men. However, in women between 55 and 70 years of age, the death rate is lower among the single than among the married.

A number of endogenous metabolic disorders are associated with coronary artery disease—uncontrolled diabetes, hypothyroidism, and xanthomatosis to mention a few. In diabetes particularly, generalized atherosclerosis is important as a cause of death, even when the diabetes has been under control for many years.

A hormonal approach to the problem has been suggested frequently, because coronary artery disease is less prevalent among middle-aged women than men and also because of evidence that estrogens lower blood-cholesterol. Thyroid extract also depresses lipoproteins but at the expense of increased metabolism and circulation. If new compounds can be isolated from thyroid hormones that depress the blood fats without increasing metabolic rates, as suggested by the work of Trotter and Goolden,[10] this would be another lead well worth pursuing.

Until recently, coronary artery disease was considered as the inevitable process of tissue aging and deterioration. But research on deranged fat metabolism and dietary intake has challenged this concept. This will be discussed in more detail under the heading of nutrition and coronary artery disease.

ALCOHOL, TOBACCO, AND INFECTIONS

The relevance of alcohol and tobacco to coronary artery disease comes largely from statistical studies of large population groups in fields other than heart disease; these studies provide no definite conclusions. It was from studies of the use of tobacco and the incidence of cancer of the lung that incidental findings were reported of higher death rates from coronary thrombosis among heavy smokers than among nonsmokers.

Clinically, it has been customary to advise against smoking for persons with coronary artery disease but, on the contrary, to encourage the use of alcoholic drinks for their relaxing effects, especially brandy, before meals and at bed time. There is no evidence in the medical literature to support or deny these latter practices, although there is some evidence of relationship between smoking and anginal attacks.

The role of infections in the development of coronary artery disease has received little attention, with the exception of the association of coronary artery disease and gall-bladder disease. The two conditions are often encountered in the same middle-aged males and frequently simulate one another in their initial symptomatology. Disturbances in fat metabolism are common to both conditions and certainly warrant further clinical and laboratory investigation.

MENTAL STRESS

There is no scientific basis for the clinician's impression and laymen's conviction that mental stress or emotional disturbances are predisposing to coronary artery disease. The role of emotional stress as an immediate precipitator is also in doubt; many persons with coronary artery disease die quietly in sleep. Yet one must not discard psychosomatic theories in coronary artery disease simply because no conclusive studies are available. These problems are exceedingly complex ones to study. Assessment of psychologic factors is difficult even in the field of psychiatry.

The psychologic symbol of the heart, in the minds of both sick and well persons, adds a complicating feature to any investigation of the relationship between the emotions and other nervous mechanisms associated with various forms of heart disease. The individual who has suffered an attack of coronary artery disease is often profoundly convinced that mental stress played an important role in predisposition to or precipitation of his disease. This is purely subjective, to be sure, but it may also be a clinical clue that is worthy of pursuit on a systematic objective basis. We do not yet possess sufficient evidence, either positive or negative, to rule out mental stress as an important factor in the occurrence or progression of coronary artery disease.

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HIGH BLOOD PRESSURE

Studies in man and animals indicate that increased intravascular pressure is associated with atherosclerosis but not alone of the coronary arteries. Furthermore, autopsy material on persons with a history of high blood pressure does not consistently show coronary atherosclerosis or evidence of myocardial damage. In post-mortem findings, cerebro-renalvascular diseases are often associated with a history of sustained high blood pressure. High blood pressure, then, may be a factor in the development of coronary artery disease but its importance as a precursor or precipitator is unknown. In studies of this aspect of the problem, the extent to which high blood pressure contributes to coronary artery disease is infrequently related to the time of initiation and the duration of sustained elevated levels, and to the height of the blood pressure, with variations by age, sex, and other characteristics of the population under study. Unfortunately, there are no international criteria for a diagnosis of high blood pressure or even standard methods for obtaining uniform measurements. Again, comparison of studies from one country to another under these conditions is of dubious value.

PHYSICAL ACTIVITY AND OCCUPATION

The medical literature abounds with articles that purport to show different frequencies of coronary artery disease among various social and economic groups. It is often stated that business and professional men become victims of coronary artery disease not only more often but with greater severity than other men. The scientific evidence is very sketchy on this point. Associated factors such as diet, obesity, mental stress, and physical activity are either ignored or mentioned only briefly.

The careful studies of Morris[11] in England indicate that physicians have a higher risk of morbidity and mortality from coronary artery disease than other men and that general practitioners are worse off than specialists. His studies on persons in the same economic class give evidence that those who have a higher degree of physical activity experience a lower degree of morbidity and mortality from coronary artery disease. He suggests that habitual physical activity in work may be a protective factor against coronary artery disease, particularly against the rapidly fatal first attacks. He found that London bus conductors who go up and down the stairs continuously had only half the "sudden death" rate of the sedentary drivers of the buses. Other studies in the United States, notably Stamler's,[12] give evidence of a higher coronary artery disease death rate among laborers.

It is reasonable to assume from the literature that physical activity is a significant factor to be considered in epidemiologic studies; one must observe how it varies with mode of life, especially the diet, overweight, and occupation. Its priority position in the chain of evidence of cause and effect in coronary artery disease is not known.

Physical activity has special significance in the study of treatment of coronary artery disease because of self-imposed as well as clinical limitations. In recent years some cardiologists, e.g., Levy,[13] have tended to relax these limitations on the basis of satisfactory results in clinical practice.

BLOOD COAGULATION AND THROMBOSIS

There is experimental evidence that blood coagulation may be influenced by diet and other factors, especially from studies on the heparin-lipoprotein systems. Studies of blood-clotting mechanisms have shown a relationship with fat content of the blood, particularly after meals, and with fat transport. The clearing of fat from the blood after a meal appears to involve a lipoprotein enzyme and depends for its specific action on the presence of triglycerides of lipoproteins, chylomicra, and heparin (Korn[14] and Anfinsen[15]). The cholesterol-phospholipid ratio may be implicated in this mechanism also. Increased lipids in the blood after a fatty meal appear to make the blood more coaguable which, in turn, may have a direct bearing on the development of thrombosis in the coronary arteries.

Duguid[16] has found many persons whose deaths from coronary artery disease were primarily on the basis of thrombosis rather than atherosclerosis. He is of the opinion that thromboembolic phenomena are more important factors in the etiology of coronary artery disease than is commonly recognized and warrant more extensive investigation. He has revived interest, too, in Rokitansky's hypothesis of over 100 years ago of "encrustation" in the pathogenesis of atherosclerosis.

His histologic surveys show that arterial thrombosis is much more common than is generally supposed. Lesions classified as atherosclerosis may be, in reality, altered thrombi. Duguid believes there may be two forms of atherosclerosis: one arising from thrombosis, the other from primary fat deposits in the arterial intima. Once the initial stage is set of fatty streaking, a vicious cycle of mural thrombosis and attendant fatty change and then further mural

thrombosis ensues. The impairment of the coronary circulation occurs when thrombosis is sufficient to narrow the coronary arteries. So in considering the etiology of atherosclerosis as a clinical condition, Duguid thinks attention must be turned to the blood and the factors which govern thrombosis.

Morris believes also that clotting and thrombosing mechanisms should be a major focus of investigation in coronary artery disease.[17] He further observes that post-mortem studies show that only a minority of men with much or severe coronary atheroma actually suffer infarction and also that some with little evidence of coronary atheroma can have serious obstruction and ischemic heart disease.

To complicate the relationship of thrombosis and coronary artery disease still further, Bronte-Stewart and his co-workers[18] observed improved lysis of blood clots if exercise occurred after ingestion of fat. Multiple factors most certainly must be sorted out and evaluated in the study of the relationships of blood coagulation, blood lipids, diet, and other factors with coronary artery disease.

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NUTRITION

The probability of multiple etiology and manifestations of coronary artery disease has stimulated a vast amount of research over the years in the nutritional aspects of the problem. Nutrition itself is a complex subject in the human being; knowledge is still limited as to some food elements that presumably are essential to life or whose overabundance or deficiency leads to disease or dysfunction.

Strangely enough, data on type and quantity of food intake prior to attacks of coronary artery disease are sparse for representative serial segments of the population. Large population groups are difficult to observe over long periods of time, yet without these observations, one cannot obtain significant base lines for the incidence and prevalence of the various nutritional characteristics under scrutiny. Even if the intake of food elements varies in a similar fashion to morbidity and mortality of coronary artery disease, it is not proof of a causal relationship; associations encountered may be due to common effects of entirely unknown or unsuspected factors.

Atherosclerosis can be experimentally produced in several animals by dietary manipulation, but there are major differences in metabolic response to the same diet among different species. Levels of total serum cholesterol and lipoprotein cholesterol can be changed by dietary modifications in animals. But it has not been possible to produce coronary artery disease selectively in experimental animals by dietary manipulations, although generalized atherosclerosis has been produced in different species. The work of Stare and his colleagues[19] on monkeys is noteworthy. Nor can results of studies in animal populations be extrapolated directly to human populations; this is true in atherosclerosis, as it is in so many other diseases.

Bearing in mind the limitations of using heart disease mortality rates for comparative purposes, it was observed during the last war that countries with enforced reduction of food intake, especially fats and proteins, had a decreased mortality rate for coronary artery disease. These are significant clues but only leads for further study. It must be repeated that diets were not the only factors

in modes of living and the environment that were forcibly changed during the war years, but they were more easily measurable than the other changes and accordingly given greater attention and study.

OBESITY AND OVERWEIGHT

Dietary imbalance has been implicated by many observers as an important causal factor in coronary artery disease. Obesity and overweight are not identical although many articles in the literature consider them equivalent. Obesity refers to an excess proportion of the body weight being made up of fatty tissue; overweight refers to the state of being above a predetermined standard according to age, sex, and height. These are both relative terms. One can be obese without being overweight and, conversely, overweight without being obese. Obesity and overweight vary with skeletal type, physical activity, eating habits, and other personal and group characteristics. Again, it is not easy to identify exact relationships between overweight and coronary artery disease because one is dealing with only two of many presumably interdependent variables.

The Committee on Nutritional Standards of the Food and Nutrition Board of the National Research Council of the United States of America[20] has recommended suitable standards for selected items of physical measurements which should have usefulness in distinguishing body fatness from levels of overweight in future studies of heart disease.

There is no convincing evidence that relative obesity is a major factor in coronary artery disease. Obesity is not rare among persons who live into old age without evidence of this disease; this is true in many countries. Nevertheless, obesity does add a mechanical burden to the cardiovascular system including fatty infiltration of the heart muscle itself. For this reason, its role in epidemiologic studies is of concern for general health reasons.

Overweight also adds a burden to the cardiovascular system and is associated with increased food intake and, frequently, increased proportion of fat in the diet. What role it plays as a precursor of coronary artery disease is difficult to define because of our lack of knowledge of the development of hidden coronary atherosclerosis among persons of differing body weights throughout their early adult and middle years. Survival-rate studies made by insurance companies show a decreased rate of survival of middle-aged males who are overweight at the time of initial physical examination. But we have no comparable data on the survival rates of such individuals related to fat in the diet and the amount of coronary artery disease. It is when we try to link up fat in the diet to fat constituents in the blood to coronary artery disease that we are confronted with many missing links in the chain of cause and effect.

FATS IN THE DIET

The relationship between fats in the diet and in the blood has been a subject of intensive investigation for many years and more recently of highly intense and even emotional controversy among medical and nonmedical scientists, especially the role of fat metabolism in the etiology of atherosclerosis. The tremendous industrial as well as personal and professional implications may explain some of this intensity of feeling.

Keys and his co-workers[21] have done a prodigious amount of research on selected samples of population groups in many parts of the world in an effort to show that the amount and type of dietary fat determine the lipid constituents of the serum and that these in turn may affect the development of atherosclerosis. They have shown by controlled experiments in man that changing the proportion of calories supplied by fats results in significant changes in the total serum cholesterol. Their evidence is convincing on this relationship; although Mann does not concur in this opinion,[22] nor do the Gofman associates.[23] No group has successfully reconciled these divergent points of view up to the present.

Keys[24] is firmly of the opinion that a most important clue to the solution of the coronary problem is the differing frequency of the disease in populations that differ in their modes of life. Most epidemiologists agree with this statement, but they point out that this is a clue only and not the complete profile of the criminals at work in the coronary arteries.

As cholesterol is the chief constituent of atheromatous plaques found in diseased coronary arteries, it is only natural to try to determine what proportion of individuals with various stages of coronary artery disease have elevated blood levels of cholesterol. If atherosclerosis is a disorder of lipid metabolism, this phase of the problem is worthy of the extensive exploration it has had. Investigations over the years have given varied results.

Here is a recent example of such a critical study from our own research center in the Albany Medical School. In a series of 115 white males aged 40 to 55 years, of comparable racial, economic and occupational status, Doyle and co-workers[25,25a] made comprehensive studies of the blood lipids of 40 normal individuals, 27 free of coronary artery disease but with histories of overweight, hypertension, or diabetes mellitus, 20 with a diagnosis of angina pectoris, and 28 men whose difficulty had been diagnosed as authentic myocardial infarction. All of these persons were working full time as state employees. The total serum cholesterol was significantly increased in the myocardial infarction group, with the increases found principally in the beta-lipoprotein cholesterol portions of the blood (Table II). The wide overlap of values from the coronary artery

TABLE II. AVERAGE SERUM LIPOPROTEIN-CHOLESTEROL (MG. PER 100 ML.)

		TOTAL	ALPHA	BETA	PER CENT BETA
Normal	Mean ± SD	244 ± 41	37 ± 11	194 ± 44	84 ± 6
	Range	159 – 358	14 – 59	113 – 330	72 – 94
Suspect	Mean ± SD	229 ± 48	37 ± 10	186 ± 47	83 ± 6
	Range	168 – 333	15 – 62	118 – 282	68 – 93
Angina pectoris	Mean ± SD	251 ± 44	33 ± 7	213 ± 42	86 ± 5
	Range	192 – 352	17 – 50	165 – 305	78 – 93
Myocardial infarction	Mean ± SD	288 ± 51	39 ± 10	238 ± 51	86 ± 4
	Range	199 – 405	19 – 59	137 – 352	73 – 92

disease group to the normal one obviates any predictive significance to individual readings. (For example, the normals in this study have a mean serum lipoprotein cholesterol of 244 mg. per 100 c.c. ± standard deviation of 41, the myocardial infarctions, 288 mg. per 100 c.c. ± S. D. of 51. The overlap is apparent.) (Fig. 3.)

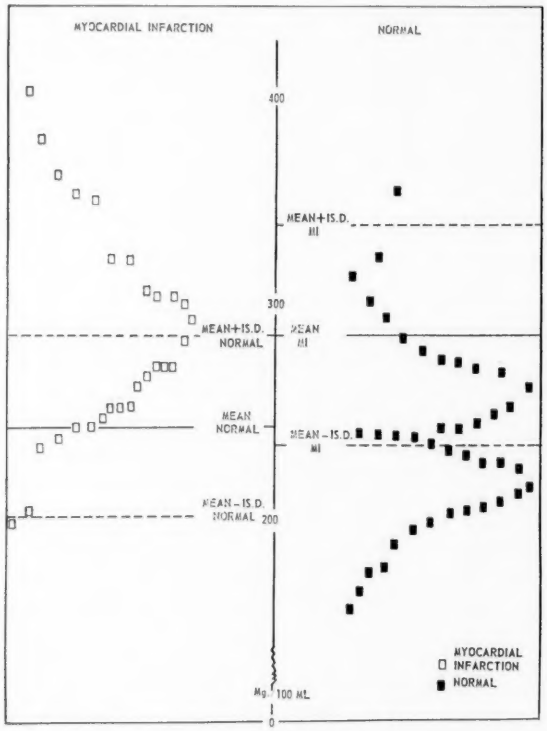

Fig. 3.—Total serum lipoprotein cholesterol milligrams per 100 ml.

Individuals with angina pectoris, alone, showed blood lipid patterns no different from those of the normal persons in the study. As Master[26] has recently noted, this again poses the question of the significance, both clinically and pathologically, of angina pectoris.

Doyle's group also concluded that total serum cholesterol provided as much information, or as little, as other more elaborate procedures, for measuring lipid constituents of the blood, including the ultracentrifugal characterization of serum lipoproteins.

Gofman and co-workers[27] claim that the serum content of certain classes of blood lipoproteins varies not only with the quality and quantity of fat but also with the proportion of carbohydrates in the diet. They question whether the changes in the serum cholesterol are adequate indices of serum lipid variations. They have commented that the risk of coronary artery disease is intimately related to both classes of lipoproteins, Sf 0-20 and Sf 20-400; they claim that

they can predict from blood samples, so tested, the risk of developing coronary artery disease in an individual. The medical literature abounds with the reports of competent scientists who disagree with the Gofman views. Therefore, the relationship of total calories, of fatty diet, and blood lipids is far from clear-cut.

Some investigations have proposed the administration of plant steroids, like sitosterol which interferes with the absorption of cholesterol,[28] to reduce the possibility of developing atherosclerosis. Long-term follow-up studies have not been done on population groups taking quantities of these materials, so we have no end results to evaluate. This work, however, may afford some clues on lipid metabolism in the genesis of coronary artery disease.

Still one other phase of the fat story must be mentioned because of its potential yet unsubstantiated public health importance; reference is made to the relationship of unsaturated fatty acids in the diet to atherosclerosis.

Although Evans and Burr[29] in 1927, and Burr and Burr[30] in 1929, showed that the unsaturated fatty acids, linoleic and arachidonic, were essential in rats to maintain growth and to avoid dermatitis, no definitive data have been presented in the intervening years to show relative or absolute essentiality of the unsaturated fatty acids in the human body. In England, Sinclair[31] has recently speculated that relative deficiencies of these acids and a low intake of vitamin B_6, coupled with a high intake of saturated fatty acids, predispose one to a variety of degenerative disorders, including atherosclerosis.

The question comes up again as to the kind and quantity of dietary fats that might lead to increased blood lipids and that might lead to atherosclerosis. Recent interest has been intensified from the publications of Ahrens, Blankenhorn, and Tsaltas[32] and of Bronte-Stewart and colleagues[18] of evidence from human trials that the serum cholesterol levels are depressed, by feeding dietary fats, in which a high proportion of the fatty acids are unsaturated, i.e., corn and other vegetable oils and those from fish and marine mammals. This lowering of serum cholesterol occurred even in the presence of saturated fatty acids in the diet. The problem of determining which unsaturated fatty acids might be essential is involved in this whole question too. These workers, however, do not identify an essential substance in the unsaturated fatty acid diets or explain the mechanism that lowers serum cholesterol levels in man.

So there still remains a hiatus in the relationship between fatty diet and increased blood lipids and a gaping chasm in the relationship between blood lipids to coronary artery disease.

In 1952, Groen and co-workers[33] anticipated the studies of Bronte-Stewart's group in a classical research study in Amsterdam. They found that a vegetable diet lowered the serum cholesterol levels. They concluded "an exclusively vegetable diet reduces the blood cholesterol even if the fat content of the diet is rather high, viz., varying between 90 and 125 Gm. per day. . . ." The authors did not conclude that the changes were due to dietary fat differences, although they included this possibility along with animal proteins and total calories. Beveridge, Connell, and Mayer,[34] in Canada in 1954, showed conclusively, in short-term experiments, that type and quantity of dietary fat influenced blood lipid levels. They said "in animal fat a factor or factors act to

elevate plasma cholesterol levels and a factor or factors act in corn oil to depress plasma cholesterol levels."

Malmros and Wigand,[35] in 1955, described similar experiences and concluded "the favorable results obtained with corn oil might possibly be due to the abundance of essential fatty acids in this kind of fat."

The relation between fats in the diet and coronary artery disease has been so dramatized in the public and professional press that we can rest assured that clinical trials of the effects of unsaturated fatty acids on blood lipid levels and coronary artery disease will be intensified on a mass scale. We shall await definitive results with interest and hope.

DISCUSSION

In this discussion of critical factors involved in coronary artery disease certain questions require answers now. Is the epidemiologic evidence substantial enough to convince clinicians and public health workers to change their present attack on coronary artery disease because of recent research findings? Is the medical profession justified in recommending a revolutionary change in our eating habits on the scientific evidence presented? After reviewing the published data, the epidemiologist's answer to both questions is an unequivocal "No."

Scientific knowledge is not complete enough at present to postulate with certainty the evolution of fatty diets to blood lipids to atherosclerosis to coronary artery disease. Until more links are forged and fastened together to complete the chain of cause and effect in coronary artery disease, those of us who have the responsibility to apply new knowledge in public health practice must not proceed too far too fast.

In a report to the Council on Foods and Nutrition of the A.M.A. on Fats in the Diet in Relation to Atherosclerosis, May[36] gave some sound advice, "The present situation demands that the public receive guidance from competent physicians in the interpretation of the existing but fragmentary knowledge that seems to bear upon the problems of arteriosclerosis and coronary heart disease. Exploitation of incomplete knowledge by industries for the purpose of competition, or by investigators for personal recognition, would be irresponsible and detrimental to progress in conquering these major afflictions."

Some new and exciting clues are being exploited. We need additional follow-up studies on adequate probability samples of population groups exposed to the risk of coronary artery disease under differing conditions of living and environment in different parts of the world; we need expanded studies of random population samples that will explore several factors at the same time—diet, physical and mental activity, blood lipids, and clotting mechanisms—to mention a few that have shown promise. Fundamental studies are needed to develop standard criteria for the classification of heart diseases and for their diagnostic characteristics. Accumulated records on fat and protein levels in samples of normal and diseased populations could provide new information on relationships leading to coronary artery disease if care were exercised in setting up and carrying out studies on an epidemiologic basis.

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Let us not forget, also that there are nutrients other than fat that may be implicated in the unsolved puzzle of the cause and course of coronary artery disease. As Morris[11] has pointed out "It is a reasonable proposition that several causes and several mechanisms are involved in the human disease . . . in terms of morbid anatomy alone, different factors may operate at different stages in the long journey from flecking of the coronary arteries to the fatal heart disease—age at one stage, 'social class' at another, physical activity of work at yet a third."

So it would appear sensible at this time for physicians to advise the public and their patients that they arrange their mode of living to make full use of present knowledge of diet, physical and mental stress, and other factors that appear related to the maintenance of a healthy circulation.

People who are overweight are commonly advised to cut down on total calories—which can be done effectively by cutting down on fat intake—until weight levels are near the accepted standards. Such action reduces the physiologic burden on the heart and circulation and appears to improve well-being, no matter what its long-term benefits may be. We cannot ask people to cut down on their intake of specific fat elements in the diet for the purpose of bringing down their blood lipid levels when we don't know abnormal or presumably dangerous levels of the several blood lipid fractions in the human being in various parts of the world, living in different environments, under varying modes of life.

What criteria do we have for diagnosing hyperlipemia in the human species? There are no accepted standards. At what levels and under what conditions does hyperlipemia result in lipoidosis of the coronary arteries and lead to disabling or fatal thrombosis or occlusion? We will not know until we possess more knowledge than we have now. Therefore, it is premature for medical societies and health departments to embark upon health education programs to modify fat intake qualitatively which, by implication at least, falsely promises a reduced risk of coronary artery disease in the individual. In addition, one should exercise great care in disseminating among the general population, as if they were established truths, the tentative results of recent research bearing on a life-and-death complex like heart disease. On the other hand, the use of health education materials and techniques to bring accurate and current information on the technical aspects of coronary artery disease to the public and the health professions is highly desirable for the maintenance and improvement of the public health.[37]

CONCLUSIONS

The group of experts that met in Geneva, Switzerland in November, 1955,[1] at the request of the World Health Organization considered fully the application of our knowledge on atherosclerosis and ischemic heart disease to national and local public health programs. (Members are listed in Appendix A; in this presentation I have drawn generously on the views expressed by this study group.) The group concluded that there was no clear-cut scientific evidence to show that any particular factor causes or contributes measurably to the development of coronary artery disease. No new discoveries or developments have been made since that time to alter this viewpoint.

During the past year there have been numerous public statements by scientific and other writers that give the impression that the atherosclerosis problem has been largely solved. The chief culprit is purported to be the fat in the diet. According to these opinions all one has to do to mend the situation is to change one's eating habits so as to include a certain kind of low-fat diet. Unfortunately, scientific proof of a causal relationship between fats in the diet, the blood lipids and coronary artery disease is still lacking, although there are promising clues.

As Katz[88] and his colleagues have wisely pointed out, "Clearly significant progress has been made toward our goal, a scientific understanding of the atherosclerosis problem . . . the goal is perhaps in sight, but it has not yet been reached. Like an iceberg, more is hidden than is seen."

The wisdom of moderation is still the mainstay of therapeutic medicine, and this applies to the use of fancy diets as well as new drugs in coronary artery disease. Until further research gives us greater insight into the cause and nature of coronary artery disease, we must continue to apply existing knowledge intelligently and with diligence. Sound medical practice teaches us not to go overboard for every new food fad.

From our own studies, from the literature reviewed and from personal discussions with leading research scientists working in this field, I would make the following *assumptions:* (1) Liberal caloric intake and fat in the diet appear to be associated with increased blood lipid levels in human beings under varying modes of life. (2) Human diets with unrestricted fats, especially some of the saturated fatty acids, appear to be associated with coronary atherosclerosis, particularly in adult males but this is not a causal relationship. (3) Blood lipids, especially cholesterol beta lipoprotein fractions, appear to be higher in groups of persons with myocardial damage compared to normal persons, although the range of values found shows considerable variation and overlap in both groups. (4) Adult females, prior to menopause, are not affected with coronary atherosclerosis nearly as much as males, nor do they have anywhere near as much myocardial damage. (5) Other factors, especially blood coagulation, constitution, overweight, hormones, physical exercise, and mental stress appear to have significant roles in the development of both coronary atherosclerosis and myocardial damage.

These are merely assumptions based on the best existing knowledge. They should be used to form hypotheses for field testing. It may be that blood lipids are the basic ingredients in the production of atherosclerosis of the vascular tree and, like viruses that lie dormant for years in the central nervous system, become active in the production of coronary artery disease under the stresses of certain life experiences.

Here is one working hypothesis based upon the above assumptions: abnormal levels of blood lipids or deranged lipid metabolism appear to be predisposing to the development of atherosclerosis in the human being, but other factors in the mode of living or environment, singly, in combination, or generally, additive, must come into play before myocardial damage occurs in the susceptible individual. Thrombosis, superimposed on atherosclerotic changes in the coronary arteries may be the final insult that results in myocardial damage; throm-

bosis follows disturbances in blood coagulation which may be dependent on a variety of other factors. If this proves to be true, it would help to explain the well-being of a legion of individuals who go through life and die with marked coronary atherosclerosis but no former clinical evidence of myocardial damage.

What are these stresses, working singly or in combination, and what are the circumstances under which they cause damage to the coronary arteries and the myocardium? Are these "trigger" mechanisms that we do not understand, yet strongly suspect from the leads at hand? In other words, deranged lipid metabolism could be a predisposing factor in the development of atherosclerosis, but the mechanisms that transform atherosclerosis or thrombosis of a coronary artery into myocardial damage in selected individuals may be any of a number of factors in the individual's environment or mode of living. Some shrewd detective work in the form of epidemiologic studies should help us to identify these precursors and precipitators of coronary artery disease. We urge that research be pressed forward with all the means and personnel that can be mustered so that we may learn more about the control of coronary artery disease and eventually that we may know its causes.

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APPENDIX

W.H.O. Study Group on Atherosclerosis and Ischaemic Heart Disease
(Geneva, Nov. 7-11, 1955)

Members:

1. Monsieur le Docteur E. Aujaleu, Directeur de l'Hygiène sociale, Ministère de la Santé publique, Paris, France.
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STUDIES OF SERUM CHOLESTEROL AND LOW-DENSITY LIPOPROTEIN LEVELS, PREVIOUSLY LOWERED BY A REDUCED FAT INTAKE, AFTER THE ADDITION OF CORN OIL TO THE DIET

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THERE is widespread interest in the varying effect of animal and vegetable fats and oils upon serum lipids and lipoproteins. Opinions varied several years ago,[1-3] but more recent evidence[4-9] indicate that unhydrogenated vegetable and marine oils, low in content of saturated long-chain fatty acids and containing a high percentage of unsaturated fatty acids, do not elevate the blood cholesterol. Some results suggests that the ingestion of large amounts of vegetable oils lowers serum cholesterol even when animal fat consumption is maintained[8,9] and that corn oil may contain a factor which tends to depress cholesterol levels.[9,10]

In most of the studies mentioned there was a marked or total reduction of animal fat intake coincident with the feeding of vegetable oils. It is difficult to decide whether the beneficial effects observed in serum cholesterol levels are the result of decreased animal fat intake or are due to the increased supply of vegetable oils. Most of the diets administered were quite artificial and not likely to be followed for a long time by the average patient. It seemed desirable to determine the effect of a vegetable oil as it would ordinarily be used in salads and cooking processes in a group of private patients whose serum lipids and lipoproteins had been lowered by a previous reduction in their animal fat intake.

The subjects used in this study had been on a moderately reduced animal fat intake for several years. No patient was selected unless lowered cholesterol and low-density lipoprotein levels, as shown by at least two determinations of each lipid parameter, had been consistently maintained for at least one year prior to the addition of the oil to the diet. One patient with xanthomatosis tendinosum was included who had not responded to diet and whose lipid levels were fluctuant. The diet the patients had followed contained approximately 40 to 50 Gm. of fat daily. Eggs had been allowed in moderation (six eggs a week), but milk fat and butter had been eliminated and meat fat sharply re-

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TABLE I. SERUM CHOLESTEROL AND LOW-DENSITY LIPOPROTEINS ON NORMAL DIET, ON LOWERED ANIMAL FAT INTAKE, AND AFTER ADDITION OF CORN OIL

PATIENT	REGIME	CHOLESTEROL	SF 0-12	SF 12-400	A. I.*
1. 45 years Normal	Control	240	339	325	91
	Control	249	362	356	99
	Low fat diet—6 mo.	182	300	116	50
	Low fat diet—1 yr.	210	341	88	49
	Corn oil—4 mo.	223	286	108	47
2. 47 years Normal	Control	360	399	527	132
	Low fat diet—6 mo.	261	401	194	74
	Low fat diet—1 yr.	246	374	211	74
	Corn oil—3 mo.	240	459	165	75
	Corn oil—9 mo.	253	429	183	75
3. 54 years Coronary Atherosclerosis	Control	299	340	465	116
	Control	305	434	368	108
	Low fat—1 yr.	288	467	280	96
	Low fat—2 yr.	253	476	244	90
	Corn oil—6 mo.	316	527	323	109
4. 41 years Normal	Control	254	545	272	102
	Low fat diet—6 mo.	204	330	110	52
	Low fat—1 yr.	197	310	147	57
	Low fat—2 yr.	173	356	200	71
	Corn oil—6 mo.	206	345	218	73
5. 48 years Normal	Control	280	364	267	83
	Low fat diet—1 yr.	191	408	105	59
	Low fat—2 yr.	210	340	153	61
	Low fat—3 yr.	230	337	118	54
	Corn oil—6 mo.	156	335	141	58
6. 49 years Normal	Control	267	460	197	80
	Low fat diet—6 mo.	201	410	80	56
	Low fat diet—1 yr.	216	399	41	47
	Corn oil—3 mo.	225	392	36	45
	Corn oil—9 mo.	220	370	60	48
7. 55 years Hypertension	Control	265	695	393	159
	Low fat diet—6 mo.	198	569	377	123
	Low fat diet—1 yr.	247	443	425	119
	Low fat—2 yr.	202	399	416	113
	Corn oil—3 mo.	249	516	432	127
8. 56 years Diabetes	Control	260	303	318	86
	Control	249	435	235	85
	Low fat diet—6 mo.	184	280	101	46
	Low fat diet—1 yr.	196	310	144	56
	Corn oil—6 mo.	181	419	149	68
9. 32 years Xanthomatosis	Control	700	1010	92	117
	Control	464	797	118	100
	Low fat diet—6 mo.	492	520	238	93
	Low fat diet—1 yr.	711	910	146	116
	Corn oil—3 mo.	449	1068	134	130
10. 51 years Coronary Atherosclerosis	Control	331	580	374	123
	Control	318	610	326	118
	Low fat diet—6 mo.	273	493	296	101
	Low fat diet—1 yr.	237	486	327	106
	Corn oil—6 mo.	209	481	344	108

TABLE I.—CONTINUED

PATIENT	REGIME	CHOLESTEROL	SF 0-12	SF 12-400	A. I.*
11. 59 years Normal	Control	244	412	241	83
	Low fat diet—6 mo.	210	309	220	69
	Low fat diet—1 yr.	169	297	191	63
	Corn oil—3 mo.	168	290	174	58
	Corn oil—9 mo.	172	286	190	63
12. 42 years Normal	Control	327	461	369	111
	Low fat diet—6 mo.	214	304	162	59
	Low fat diet—1 yr.	221	340	151	60
	Corn oil—3 mo.	206	321	166	61
	Corn oil—9 mo.	231	369	141	62

$$\text{*Atherogenic Index} = \frac{\text{Standard Sf 0-12 lipoproteins} + \text{Standard Sf 12-400} \times 1.75}{10}$$

duced. The previous diet was continued unaltered, and corn oil* was added to be freely used in salads, cooking, baking, and frying. The estimated consumption, based upon the amount of oil used for the entire family, was 1 to 2 tablespoons (15 to 30 Gm.) daily for each individual. Serum cholesterol was measured by the method used in this laboratory for several years,[11] and low-density lipoproteins were ultracentrifugally determined.† The latter analysis is desirable since it quantitatively defines the various lipoprotein classes which differ in their neutral fat content particularly and may not be uniformly affected by dietary, hormonal, and enzymatic factors involved in fat transport and metabolism.

Results are presented in Table I. Control values were taken prior to the institution of lowered animal fat intake. In all, 12 patients were studied, with the period of administration of corn oil varying from 3 to 9 months. In 10 individuals, previously lowered lipid values were not substantially altered following addition of corn oil to the diet. In one of these subjects, (Patient 5) it may be that serum cholesterol dropped as a result of corn oil intake. There was only one observation, however, and lipoprotein values in this case did not fall concomitantly. In one individual (Patient 3) both cholesterol and lipoproteins apparently rose to the control levels of the corn oil regimen. In the patient with xanthomatosis (Patient 9) no result can be attributed with certainty to corn oil consumption in view of the highly variable prior lipid values. Although the values are not shown, there was very little fluctuation in weight of the group, the maximum being a 4 pound gain in one individual.

*Manufacturer's analysis: glycerides, 98.1 per cent; nonsaponifiable matter, 1.9 per cent; free fatty acids, 0.03 per cent; phospholipids, trace; iodine number 125. Component fatty acids: linoleic, 56.2 per cent; oleic, 30.1 per cent; palmitic, 9.9 per cent; stearic, 2.9 per cent; hexadecenoic, 0.5 per cent; myristic, 0.2 per cent; above C18 0.2 per cent. Component glycerides: mono-oleodilinolein, 49.2 per cent; monosaturated dilinolein 34.2 per cent.

†These analyses were performed at the Institute of Medical Physics, Belmont, Calif.

DISCUSSION

The findings of this study are interesting because the subjects are typical of those seen in private practice, the animal fat content of the diet was not restricted so rigidly that few patients would adhere to it, and the amount of vegetable oil was limited to that quantity which would replace other fats normally used in salad dressings, cooking, baking, and frying. The patients had been closely observed for several years, had fairly stable lipid values on the various regimes, and were reliable. It is probable that the prescribed diet was adhered to well. In the majority (10 of 11) of these individuals the addition of corn oil to the diet for a prolonged period did not elevate serum cholesterol or low-density lipoproteins. It seems reasonable, therefore, to include this highly unsaturated vegetable oil in the diet of those patients in whom it is deemed advantageous to lower blood fats. This is desirable since a low animal fat diet will be followed by more patients under these circumstances. There is no evidence in this study that the use of corn oil in moderate amounts resulted in any further blood lipid reduction beyond that already attained by lowered animal fat intake. It has been shown[8] that the use of large amounts of vegetable oils will depress serum lipids when moderate amounts of animal fat (50 Gm. daily) are consumed for several weeks. It does not necessarily follow that additional beneficial effect of highly unsaturated oils would be maintained for long periods of time or that they would depress blood fats at all if a high animal fat intake (100 Gm. daily) was continued at the same time. In monkeys receiving cholesterol but no animal fat,[12] serum cholesterol was significantly more elevated when consumption of vegetable oil was increased, respectively, in each of two experiments, to 32 and 45 per cent of ingested calories. When the reduction of serum lipids by dietary means is indicated, the evidence supports the prescription of a markedly reduced animal fat intake and its replacement by highly unsaturated vegetable or fish oils. Hydrogenated fats should not be used since they, too, elevate serum cholesterol.[7,8]

The rise in cholesterol and lipoproteins to their control values in Patient 3 when corn oil was included in the diet illustrates that certain individuals may not tolerate even this fat well. It is wise to measure serum lipids before and following the institution of any marked dietary change since there are variations in response to fat intake. In my experience most patients, perhaps 65 to 75 per cent, will experience a definite reduction of serum cholesterol and beta lipoproteins when their animal fat intake is reduced to 40 to 50 Gm. daily. In the remainder these lipids are unchanged on this regimen. There are also some individuals, a minority, in whom blood fats are quite low according to standards in this country despite the consumption of 100 Gm. of animal fat daily. It is apparent that people differ in their capacity to handle fat much as they vary in their metabolism of carbohydrate. The organism has a biochemical mechanism for transport, removal, and metabolic disposition of ingested fat and cholesterol. At the cellular level, lipid, carbohydrate, and perhaps protein metabolism intimately intertwine. These facts should not be overlooked in the recent surge toward the use of low-fat diets in the prophylaxis of atherosclerosis.

The results of this study contribute little to our understanding of the reason for the differential effect of saturated and unsaturated fats on serum lipids. No evidence was found in the amounts of corn oil ingested by these subjects of a factor tending to depress cholesterol levels.[9,10] The rise in lipids in Patient 3 with the addition of corn oil to the diet argues against the role of a relative deficiency of essential fatty acids in the etiology of hypercholesterolemia and atherosclerosis.[13] In this connection it is pertinent to recall, as Keys has pointed out,[14] that essential fatty acid deficiency results in skin lesions and poor growth, not hypercholesterolemia and atherosclerosis.

SUMMARY

1. The effect of the addition of corn oil to the diet upon serum cholesterol and low-density lipoproteins was determined in 11 patients in whom these lipids had previously been lowered by a decrease in their animal fat intake.

2. In 10 of these patients, there was no elevation of the lipid values when corn oil was ingested in moderate amounts for 3 to 9 months.

3. In one patient both cholesterol and lipoproteins rose to control levels after the oil was added to the diet.

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THE EFFECT OF ADRENERGIC BLOCKING AGENTS (INCLUDING CHLORPROMAZINE) ON SERUM LIPID LEVELS OF PATIENTS WITH DISORDERS OF FAT METABOLISM

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AN EFFECT of chlorpromazine on lipid metabolism has been observed in two situations. In the first, two patients with essential hyperlipemia showed a rapid fall in all of the elevated lipid fractions soon after treatment was begun.[1] In the second, chlorpromazine inhibited the rise in blood cholesterol and deposition of lipid in the arteries and liver of cholesterol-fed rabbits as compared with untreated controls.[2] Both observations leave unanswered the possible mechanism whereby such an effect is achieved.

Of the various metabolic actions of the drug thus far described, none seemed adequate to account for this phenomenon. Although chlorpromazine appeared to dampen the response of dogs to burn stress,[3] parenteral administration of 25 to 50 mg. of the drug prior to surgical operation did not alter the physiologic responses of patients to surgical stress.[4] The effects on the pituitary-adrenal axis did not appear consistent enough or great enough to account for an alteration of fat metabolism. Chlorpromazine, along with a number of other anesthetic drugs, produced a significant decrease in the nonprotein sulfhydryl compounds (NPSH) of the livers of rats.[5] Epinephrine produced a similar decrease in NPSH, which was thought to represent chiefly a decrease in liver glutathione.[6] Since SH-containing compounds may impair cholesterol and fat synthesis, their decrease should not be expected to reduce serum lipids.

Chlorpromazine is said by some investigators to be a moderately active adrenergic blocking agent.[7] This action might influence serum lipid levels. Recent evidence indicates that epinephrine can increase the mobilization of fat from depots, enhancing its deposition in the liver. Adrenalectomized or adrenal demedullated rats treated with ethionine failed to develop fatty livers unless epinephrine and physiologic amounts of cortisone (in the case of totally adrenalectomized animals) or epinephrine alone (in the case of adrenal demedullated animals) was also given.[8,9] Subcutaneous administration to dogs of single large doses of epinephrine in oil produced a rise in plasma phospholipid, cholesterol,

This study was assisted by a grant from Smith, Kline & French Laboratories, Inc.

and esterified fatty acids within 24 hours.[10] Repeated small doses of aqueous solutions of epinephrine had a similar effect. Intravenous injections in rabbits of epinephrine over a 14-day period were followed by significantly greater concentrations of serum total lipids, phospholipid, and neutral fat then in control animals.[11] Accompanying these changes in serum lipids the animals developed the typical lesions of epinephrine arteriosclerosis. The production of such lesions has been blocked by the administration of two adrenergic blocking agents, ergotamine[12] and dibenamine.[13] Fat mobilization in normal animals has been reduced by ergotamine to levels observed in totally adrenalectomized rats.[9] Thus animal studies suggested that this pharmacologic action of chlorpromazine might be pertinent to its effect of lowering serum lipids in human beings.

The present study was undertaken to test the hypothesis that adrenergic blocking agents might reduce serum lipid levels in human beings. Chlorpromazine and three other adrenergic blocking agents were studied. These drugs were administered to patients with a variety of disorders of lipid metabolism while measures of serum lipids were being obtained.

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METHOD OF STUDY

The clinical characteristics and representative serum lipid levels of the 13 patients studied are listed in Table I. Eight of these 13 patients were studied as hospital patients, the others as outpatients. The abnormalities of lipid metabolism were confirmed by serial laboratory tests or had been known to exist for some time prior to the study. Five patients were psychotic, but the lability

TABLE I. CHARACTERISTICS OF PATIENTS STUDIED WITH DISORDERS OF FAT METABOLISM

CASE	AGE	SEX	DIAGNOSIS	RESENTATIVE SERUM LIPID LEVELS (FASTING)			COMMENTS
				TOTAL LIPID	CHOLESTEROL	PHOSPHOLIPIDS	
1. L.T.	32	M	Essential hyperlipemia	3,200	604	620	Fatty liver
2. J.G.	34	M	Essential hyperlipemia	3,680	412	500	Known 3 years
3. C.R.	38	M	Essential hyperlipemia	4,430	448	496	Chronic pancreatitis
4. A.B.	62	M	Diabetic hyperlipemia	3,620	589	600	No insulin
5. G.S.	29	M	Hypothyroid, postoperat.	890	361	292	P.B.I. 1.5 mcg./100 ml. untreated
6. P.H.	35	M	Xanthoma tuberosum	2,040	562	496	Biopsy confirm.
7. L.B.	32	M	Familial hypercholest.	950	324	285	No clinical signs
8. E.B.	50	M	Hypercholest.	1,710	525	483	Myocard. infarct.
9. W.M.	47	M	Hypercholest.	1,320	446	384	Myocard. infarct.
10. A.B.	25	M	Hypercholest.	1,680	513	420	No clinical signs
11. R.D.	53	F	Hypercholest.	1,340	492	400	Anginal syndrome
12. W.W.	64	M	Hypercholest.	1,049	384	315	Xanthelasma
13. M.C.	27	M	Xanthomatosis	1,910	595	510	Biopsy confirm.

of blood lipids sometimes seen in such patients was not observed in these patients during the control period. Progress was followed by determinations of total lipids, cholesterol, and phospholipids based on published techniques.[14-16] In most of the patients studied, it was possible to obtain multiple control or treatment values for lipid fractions. Arbitrarily, a reduction of 25 per cent or more in the mean treatment value from the mean control value was considered to be a fall unlikely to occur spontaneously or from extraneous factors (significant reduction). A reduction of 10 to 25 per cent was considered as equivocal but suggestive of a treatment effect.

Attempts were made during the studies to make the drug being tested the major variable introduced into the patients' regimens. Each patient continued on the same diet he customarily took. With the exception of Patient 13 (who gained 9 pounds) weights of patients remained within a 2 to 4 pound range throughout the study. If lipotrophic agents had been used previously, they were discontinued well in advance of this study. When patients were used for more than one trial of drug, a period without treatment intervened. However, it was not always possible to begin each treatment trial with the patient at the same level of serum lipids.

RESULTS OF STUDIES

The effects of treatment of 12 patients with chlorpromazine are summarized in Table II. Duration of treatment ranged from 10 days to 14 months. The

TABLE II. EFFECT OF CHLORPROMAZINE ON SERUM LIPID LEVELS IN DISORDERS OF LIPID METABOLISM

CASE	DAILY DOSE DRUG	DURATION TREATMENT	TOTAL LIPIDS MEAN (RANGE)	CHOLESTEROL MEAN (RANGE)	PHOSPHOLIPIDS MEAN (RANGE)
1.	CP		3,245(3,200-3,310)	602(584-640)	620(595-660)
	100 to 400 mg.	14 months	*1,530(1,200-1,845)	*325(215-410)	*370(325-500)
2.	CP		3,690(3,480-3,910)	474(412-590)	530(440-640)
	200 mg.	5 months	*2,310(1,530-3,160)	*327(266-378)	*385(320-430)
3.	CP		4,430	448	496
	300 mg.	15 days	*2,580(2,520-2,640)	*310(305-315)	*360(355-365)
4.	CP		3,620	589	600
	600 mg.	10 weeks	*2,555(2,310-3,140)	*445(390-470)	†485(430-535)
5.	CP		920(890-950)	351(342-361)	290
	400 mg.	8 weeks	*670	†275(260-300)	†228(222-232)
6.	CP		2,205(2,040-2,370)	572(545-610)	515(495-540)
	300 mg.	3 weeks	†1,700(1,640-1,880)	†488(420-570)	†432(400-470)
7.	CP			317(310-324)	285(280-290)
	100 mg.	30 days		322(318-326)	317(310-325)
8.	CP		1,710	552(525-566)	483
	150 mg.	10 days	*1,365	†476	443
9.	CP		1,290(1,260-1,320)	428(410-446)	376(360-384)
	150 mg.	3 months	1,245(1,180-1,340)	392(369-418)	348(317-378)
10.	CP		1,755(1,360-1,950)	526(513-540)	40(398-420)
	up to 2,400 mg.	2 months	†1,487(1,390-1,680)	†396(378-420)	†357(320-380)
11.	CP			492	400
	150 mg.	5 months		†394(371-420)	†358(330-415)
12.	CP		1,975(1,910-2,105)	650(602-695)	540(510-590)
	400 mg.	5 weeks	†1,580(1,400-1,740)	†526(403-580)	†438(400-475)

All values in mg. per 100 ml.
*25 per cent or greater reduction from mean control values.
†10 per cent or greater reduction from mean control values.

daily oral dose of drug varied from 100 to 2,400 mg. The mean values for total lipids decreased significantly in 6 patients, with equivocal reductions in an additional 3 patients. Cholesterol values declined significantly in 4 patients and equivocally in 6. Phospholipids declined significantly in 3 patients and equivocally in 6. In all, 10 of the 12 patients showed significant or equivocal reductions in one or more lipid fractions during treatment.

The early effects of treatment with chlorpromazine were most striking in patients with hyperlipemia. The response of serum cholesterol values in 4 such patients given brief initial treatment trials are noted in Fig. 1. Cases 1 and 2 were followed during a period after treatment was withdrawn. An intercurrent illness forced the termination of studies on Case 3 after 15 days of treatment. The declines were prompt and sharp in all 4 patients, the maximum effect being apparent within the first 2 weeks. Cases 1 and 4 showed some tendency for serum cholesterol levels to rise despite continued treatment. Both Cases 1 and 2 continued to have gradual rises toward initial cholesterol levels after treatment was stopped.

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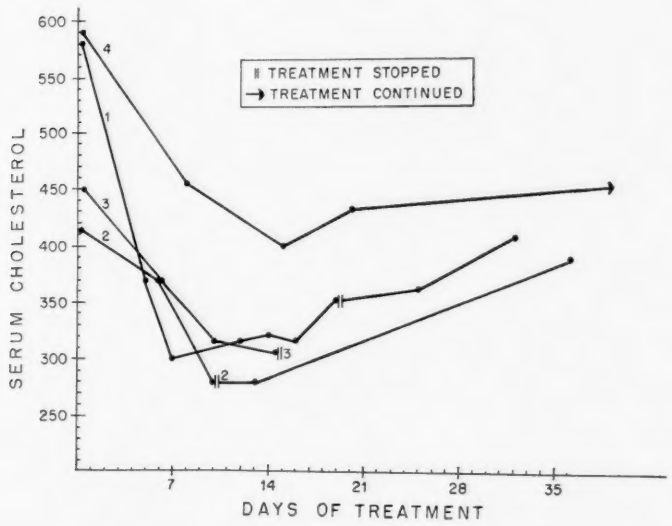

Fig. 1.—Early effect of chlorpromazine on serum cholesterol levels in patients with hyperlipemia.

The results of chlorpromazine treatment were less striking in the 8 patients with hypercholesterolemia (Fig. 2). Cases 7 and 9 never obtained convincing reductions of lipid values during treatment. The decreases in serum cholesterol in Cases 11 and 13 were of lesser magnitude and slower to appear than in the hyperlipemic patients. Stopping treatment, as in Cases 6 and 8, was followed by steady relapse. Continued treatment, as in Cases 5 and 10, maintained most of the reductions obtained.

The results of 9 trials of other adrenergic blocking drugs in 5 patients are shown in Table III. All but one of these patients had also been treated with

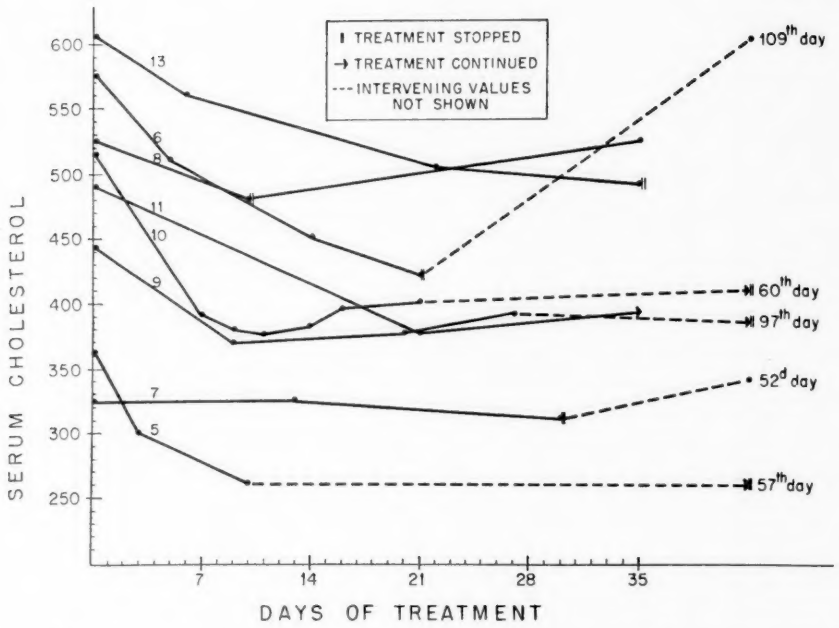

Fig. 2.—Early effect of chlorpromazine on serum cholesterol levels in patients with hypercholesterolemia.

TABLE III. EFFECT OF HYDERGINE, REGITINE, AND DIBENZYLINE ON SERUM LIPID LEVELS IN DISORDERS OF LIPID METABOLISM

CASE	DAILY DOSE DRUG	DURATION TREATMENT	TOTAL LIPIDS MEAN (RANGE)	CHOLESTEROL MEAN (RANGE)	PHOSPHOLIPIDS MEAN (RANGE)
2.(a)	Hyd.		2,325(2,230-2,430)	283(268-298)	370(360-390)
	2-4 mg.	8 weeks	2,238(1,250-3,110)	280(204-336)	373(260-440)
8.	Hyd.			532	483
	2-4 mg.	5 weeks		510(463-534)	450(430-475)
9.	Hyd.		1,360	417	375
	2-4 mg.	5 weeks	*1,186(1,100-1,245)	402(372-433)	*325(315-346)
11.	Hyd.		1,390	472(468-476)	400(390-410)
	4 mg.	2 weeks	1,440(1,400-1,506)	471(462-481)	400(375-413)
12.(b)	Hyd.-Reg.		1,061(1,049-1,074)	376(368-384)	311(308-315)
	4 mg.-150 mg.	3 wks.-5 wks.	* 864(700-971)	*314(294-354)	*258(228-290)
2.(a)	Reg.		4,170	414	490
	150 mg.	6 weeks	†2,384(1,670-3,640)	†284(242-364)	†375(305-490)
11.	Reg.		1,408(1,390-1,440)	462(432-474)	401(380-413)
	150 mg.	5 weeks	1,375(1,300-1,450)	*410(374-485)	*350(328-394)
2.(a)	Dib.		4,940	415	537
	20 mg.	7 weeks	†2,208(1,500-2,660)	†306(265-330)	†363(310-395)
9.	Dib.		1,245	433	346
	20-40 mg.	6 weeks	1,200(1,035-1,255)	*389(353-408)	339(305-360)

All values in mg. per 100 ml.
*10 per cent or greater reduction from mean control values.
†25 per cent or greater reduction from mean control values.
(a) Three separate trials at different points in course of same patient.
(b) Successive courses of each drug without interruption or treatment.

chlorpromazine. Hydergine (combined hydrogenated alkaloids of ergot) was used in 4 patients. The usual sublingual daily dose began with 2 mg. and increased to 4 mg. after the first 3 weeks of treatment. Regitine (phentolamine) was used in two patients with daily oral doses of 150 mg. being given for periods of 5 and 6 weeks. Dibenzyline (phenoxybenzamine) was used in daily oral doses of 20 mg. for 7 weeks in one patient, and 20 mg. increased after 3 weeks to 40 mg. for another 3 weeks in the second patient. One patient received hydergine 4 mg. daily for 3 weeks followed by Regitine 150 mg. daily for 5 weeks.

Only one of the four patients treated with hydergine showed an equivocal reduction in mean values for two lipid fractions during treatment (Case 9). The behavior in Case 2 was quite erratic. During the first 4 weeks of treatment with 2 mg. daily, the patient's total lipid value fell from 2,380 mg. per 100 ml. to 1,250 in 2 weeks, but rose despite treatment to 2,940 by 4 weeks. At this time, he was placed on a dose of 4 mg. daily. In another 2 weeks, his total lipids fell to 1,255 mg. per 100 ml. but they had risen to 3,110 by the end of 4 weeks at the higher dosage. This patient had not fully relapsed from previous treatment when these trials were started, making it difficult to evaluate these volatile responses.

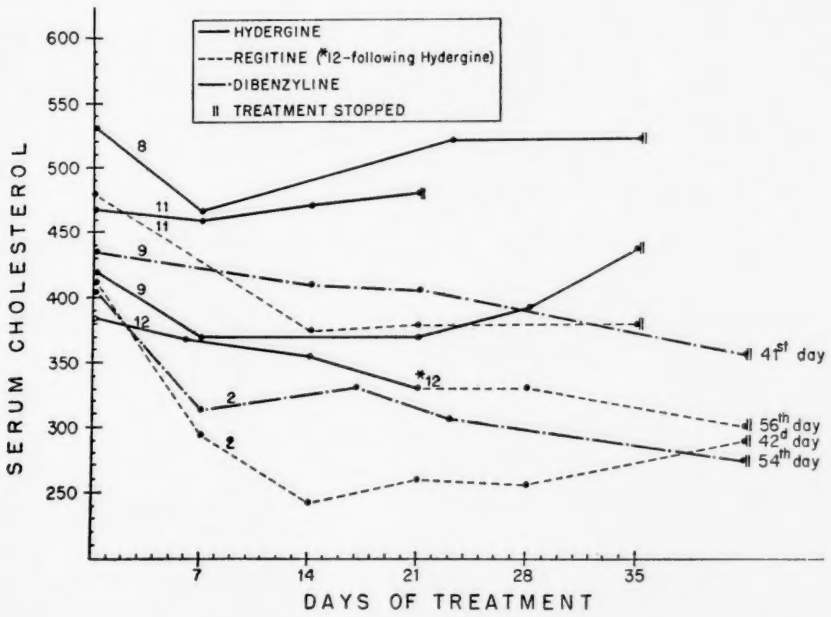

Fig. 3.—Effect of combined hydrogenated alkaloids of ergot (Hydergine), phentolamine (Regitine) and phenoxybenzamine (Dibenzyline) on serum cholesterol levels in patients with disorders of lipid metabolism.

One patient (Case 2) had significant reductions in all lipid fractions during treatment with Regitine. The other patient treated with Regitine (Case 11) had equivocal reductions in two serum lipid fractions. Most of the fall in serum cholesterol levels produced by Regitine occurred within the first 2 weeks (Fig. 3).

One patient (Case 2) had significant reductions in all lipid fractions during treatment with Dibenzyline. The other patient treated with this drug (Case 9) showed an equivocal fall only in serum cholesterol levels. The response to Dibenzyline appeared to be slightly slower than to the other drugs (Fig. 3).

The patient (Case 12) treated with successive courses of Hydergine and Regitine was considered as having a single course of treatment. This patient showed equivocal reductions in all lipid fractions. The decline in serum cholesterol was produced equally by both drugs (Fig. 3).

In general, the responses to chlorpromazine were better than to the other drugs. Likewise, responses of hospitalized patients (Cases 1, 3, 4, 5, 6, 10, 12, and 13) were generally better than outpatients. Treatment with chlorpromazine was generally more intensive in the hospitalized patients who could be kept under closer observation. It is possible that less than 200 mg. daily of this drug is an inadequate dose to produce or maintain this effect in some patients. The sublingual doses of Hydergine used in this study were probably inadequate for optimum effect. The same might have been true for the doses of Regitine and Dibenzyline used.

The short period of treatment required to produce the observed effects was thought to preclude the possibility that factors other than the drugs were responsible for these changes. With discontinuation of treatment, relapse to pretreatment levels was usually prompt. Although some patients with hyperlipemia undergo spontaneous episodes of clearing of the serum associated with acute abdominal symptoms, none of the hyperlipemic patients in this study experienced any such sequence during the trials of drug. In Case 2, we did observe such a phenomenon several weeks after discontinuation of the course of Dibenzyline.

Increasing the dose of chlorpromazine to very high levels did not increase this particular effect. Despite doses as high as 2,400 mg. daily, in Case 10, the effect on serum lipids was not appreciably enhanced, though there was a manifest increase in other pharmacologic effects of the drug. The tendency for blood lipid values to rise slightly despite continued treatment suggests the possibility of some "escape" from the effect. Such escape from adrenergic blocking effects has been observed clinically in patients with pheochromocytoma treated with Regitine.

Patients treated with adequate doses of adrenergic blocking agents generally do not praise the treatment. Phentolamine and phenoxybenzamine produce side reactions such as nasal congestion, gastrointestinal disturbance, and postural hypotension. Chlorpromazine creates in addition a degree of sedation and a feeling of lethargy which is often intolerable to many patients who are obliged to carry out a full schedule of work. The combined hydrogenated ergot alkaloids produce few reactions but the sublingual doses used in this study were probably inadequate for the fullest effect. The possibility that any of these drugs might cause hypotensive episodes must be borne in mind when treating patients with coronary disorders. No sharp declines in blood pressures occurred in our patients. Some of these side reactions might be ameliorated by concurrent use of other drugs.

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DISCUSSION

The results obtained do not establish conclusively the hypothesis that it is the adrenergic blocking action of these drugs which caused the lowered lipid levels. The fact that each of the four drugs tested had some effect suggests a common action. One which all share is that of blocking adrenergic effects. In view of the extensive literature indicating that administration of epinephrine increases serum lipids, it seems reasonable that adrenergic blockade might have an opposite effect.

A recent review of the physiology of adipose tissue emphasized the importance of neural control of mobilization of fat from depots as well as its deposition from the blood.[17] This neural control extends from the hypothalmic nuclei of the autonomic nervous system through the nervous pathways that lead directly to the innervation of the adipose cell. It also embraces the neurohumoral control of fat mobilization, as in the case of epinephrine. Thus, there appear to be many levels of neural or hormonal control. Blockade of epinephrine alone might be expected to have only a short-lived action. Central inhibition of sympathetic discharge or sympathetic ganglionic blockade might also be required for sustained or complete inhibition of fat mobilization. Reserpine, a drug with weak adrenergic blocking activity but with strong inhibition of central sympathetic tone, has recently been stated to lower ultracentrifugally determined lipoprotein fractions in aged patients.[18] If one assumes that this action is through a neural mechanism, then a different level of neural control has probably been affected.

Reservation about accepting adrenergic blockade as the sole explanation for these changes in serum lipids arises because of the fact that metal-binding agents also lower plasma cholesterol.[19] Ethylenediamine tetracetate and hydralazine, both drugs with chelating properties, have been demonstrated to produce lowered plasma cholesterol to a degree and over a time period similar to that produced by the drugs used in this study. The possibility exists that each of the four compounds studied here might have chelating actions. On the other hand, hydralazine, while having only a weak adrenergic blocking activity, probably causes depression of sympathetic nervous activity at other levels.

The particular success of chlorpromazine in these studies raises the possibility of pharmacologic actions other than the adrenergic blockade which may reduce serum lipids. Chlorpromazine, unlike the other drugs used, is a powerful sedative. Recent medical press reports of work in the Soviet Union tell of experiments in which central nervous system stimulants, such as amphetamine and nicotine, increased serum cholesterol, while sedatives, such as phenobarbital, reduced it.[20] Even if one assumes that central nervous system stimulation or depression affects serum lipid levels, the mechanism is probably explained by some neurohumoral action. A frequent observation in patients treated with chlorpromazine is a rapid weight gain associated with increased food intake. One would assume that such an effect would tend to elevate lipid levels rather than depress them. The jaundice produced by chlorpromazine is very likely allergic in origin and, like most forms of biliary obstruction, accompanied by sharply increased levels of serum lipids.[21]

At present, adrenergic blocking agents cannot be recommended as a treatment for disorders of lipid metabolism. First, the effects at the usual levels of dosage cannot be easily maintained for prolonged periods. Second, the effects of present adrenergic blocking agents are not easily tolerated by most patients and could be dangerous for some. Third, results are poorest in those patients whose lipid disorder is characterized by overproduction of cholesterol, yet these patients are most commonly encountered. Finally, much more of the mechanism of action of these agents should be known before they are used widely and without careful control.

SUMMARY

The effect of four drugs on serum cholesterol, phospholipid and total lipid values was studied in 13 patients with a variety of disorders of fat metabolism. Reductions of 25 per cent or more from mean control values as compared with mean treatment values were considered significant. Reductions of less than 25 per cent but more than 10 per cent were considered to be equivocal.

Five of 12 patients treated with chlorpromazine obtained significant reductions in two or more lipid fractions. Five other patients treated with the same drug obtained equivocal reductions. Nine trials of three other drugs were made in 5 patients. One of 4 patients treated with Hydergine had an equivocal reduction in two or more serum lipid fractions. One patient of 2 treated with Regitine obtained a significant reduction. The other obtained an equivocal reduction. One patient of 2 treated with Dibenzyline obtained a significant reduction. The other obtained an equivocal reduction. One patient treated with consecutive course of Hydergine and Regitine obtained an equivocal reduction in serum lipids.

The chief pharmacologic effect which these drugs possess in common is their adrenergic blocking action. Chlorpromazine, while not necessarily the best adrenergic blocking drug, appeared to produce the most consistent effects. This drug was used more aggressively than the others in the majority of hospitalized patients. It is possible that the doses of the other drugs were inadequate for optimum effects.

It has been postulated that epinephrine plays a role in the mobilization of fat in human beings, which was previously suggested by studies in animals. However, other pharmacologic actions of the drugs tested could have caused the changes observed. At present these observations are of more physiologic interest than therapeutic value.

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A METHOD FOR EVALUATION OF LAXATIVE HABITS IN HUMAN SUBJECTS

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ENDLESS numbers of new drugs are carried from animal screening to routine medical use by the clinical trial, a procedure that varies from collections of testimonials to crisply designed experiments as effective as any in the empiric sciences. The better clinical trials are not distributed across the whole field of therapeutics. As the discipline of clinical pharmacology grew in stature and adapted the principles of experimental design to human subjects, it has tended to concentrate on particular kinds of remedies. Nowadays it is a rare study of coronary vasodilators that does not specify control with placebo and "double-blind" evaluation of cardiac pain. In other areas of therapeutics, the majority of studies are so poorly designed that their data contain no indication as to the correctness of the conclusion. From an examination of the fine print in pharmaceutical advertising we formed the impression that laxative agents, as a group, are supported by the weakest series of studies. At the same time their sales volume is conceded to be larger than any other class of drugs (Goodman and Gilman[1]). Thus, laxatives are a logical choice for expanding the scope of clinical pharmacology.

Attention should be called at once to the study, in 1954, of Seed and Harris[2] and that of Cass and Frederik[3] in the same year, which are notable exceptions to the general rule in that scientific principles have yielded reliable data on the action of laxatives. Both, however, outline methods for study of laxative action in a restricted population, i.e., elderly patients living in nursing homes. Whether drug activity in such subjects applies to all situations can be decided only by direct test. Bioassay in animals should be mentioned, for an excellent series by Loewe[4,5] has pointed out the similar responses of man and monkey to certain laxatives. Whether such similarity extends to any new laxative is a matter for experimental test. Bioassay may be more feasible in the outpatient clinic than at the cage of the monkey.

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Interest was directed to two common problems: unwanted laxative action caused by chemicals in the public food supply, and self-prescribed laxatives taken by patients who regard themselves as constipated. This report describes a method for determining relative action of laxatives in these situations.

METHOD

Two groups of human subjects participated. In the first group were 40 normal young adults who ordinarily did not take laxatives. They were paid volunteers, medical students and laboratory assistants, aged between 19 and 33 years, 7 of whom were women. In the second group were long-term laxative users, gathered from among patients of two cardiac clinics. About 500 patients on routine clinic visits were questioned in detail about their bowel habits. In 61, constipation was a serious personal problem, with long dependence on self-administered laxatives. Only 20 of these patients supplied the final data. Each had heart disease under control; ages ranged from 43 to 78, with an average of 65; 11 of the 20 were women. For the purpose of this study we did not investigate colonic function, nor did we determine whether the condition could be described as spastic, atonic, or imaginary constipation. No alterations were made in diet, water intake, or exercise, and no colon retraining was attempted. The initial aim was to explore the method with laxative takers as they are found in practice. Later, a restricted group of particular interest might be studied.

Use of ambulant patients implies compromise in measuring drug response. Except for brief visits at long intervals, the patient is on his own; in the case of laxatives, the subject taking the drug must make all the observations. But the manner of measurement matters little, as long as the response reflects the essential goal of treatment. This type of study has a natural advantage, for its concern is not why doctors prescribe laxatives, but why patients dose themselves. Our patients indicate two reasons: to increase the number and to soften the consistency of bowel movements. In a convincing discussion Seed and Harris[2] establish the fact that number and consistency of bowel movements provide an adequate statement of the intensity and clinical value of laxative action. Secondary gain from these factors may provide for ease of defecation or relief of neurasthenic symptoms which the patient connects with his faulty elimination of waste.

Information was gathered on the daily report card shown in Fig. 1. The descriptive terms for consistency were chosen to keep the subjective scale as regular as possible, with "medium" representing the desired degree of hardness. There is no reason to assume that all patients would prefer the same consistency, nor that they would assign a particular stool to the same category. As a result, changes in consistency judgment made by the same subject were the only basis for analysis of data. Consistency was reduced to a single answer for each day so that, for example, a number of small, watery stools on one day would not outweigh 3 days in which there was no evacuation. The capability of each constipated patient in marking the card was reviewed by a doctor who was unaware of the nature of the medication, until we were confident that the patient was accurately recording the events.

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The answers that emerged from these experiments compare three preparations: an inert placebo, a standard laxative, and a compound of unknown activity. Each patient recorded the results of an equal number of days for each of the three substances. The order of administration in each patient was determined by randomization, to guard against possible influence from the sequence of dosage.

BRING THIS CARD TO CLINIC NEXT VISIT

	MAKE A MARK EACH TIME YOUR BOWELS MOVED	DID YOU TAKE OTHER LAXATIVES? WHICH ONES?	MARK HERE WHETHER BOWEL MOVEMENT WAS			
			HARD	MEDIUM	TOO SOFT	WATERY
Wednesday						
Thursday						
Friday						
Saturday						
Sunday						
Monday						
Tuesday						

Name _____ Dates _____

Fig. 1.—Daily report card for study of laxative action in ambulant subjects. Patients record each stool and make a judgment about its consistency.

The unknown material was the concentrate of a beverage containing an extract of bran.* Several users of this material had testified that it possessed good laxative action. For the experiment, it was dispensed as a concentrated solution, a tablespoon containing the equivalent of 1 cup of the beverage. The dosage was 1 tablespoonful 3 times daily in water. For the final study in constipated patients, the concentration was doubled, so that each tablespoonful yielded 2 cups of the beverage and the daily dose was equivalent to 6 cups. Placebo was a similar concentrated solution of powdered Sanka coffee and cane sugar, so that a tablespoonful was equivalent to 1 cup of Sanka coffee and ⅓ teaspoonful of sugar. For the standard, fluid extract of cascara sagrada USP was added to the placebo solution so that the daily dose was 2 c.c. for normal subjects and 4 c.c. for constipated patients. The three preparations closely resembled each other

*The unknown compound was made from a dehydrated powder in commercial use as an instant beverage and consisted of "water extract of roasted wheat, wheat bran, and molasses."

in appearance, smell, and taste. In a direct comparison it was often possible to distinguish one from another, but when time elapsed between presentation of the materials they were not readily distinguished. These three solutions were considered to be within the range of variation expected from retail pharmaceutical compounding. They were dispensed from the hospital pharmacy by coded prescriptions. The bran mixture, which fermented rapidly by bacterial action, was freshly prepared each week, and patients were instructed to keep all bottles under refrigeration. In the final test of the method, 3 kinds of capsules were made, each individually weighed. One contained 0.5 Gm. USP powdered cascara sagrada, the second 0.25 Gm. cascara and lactose q.s., and the third lactose. Caramel was used to tint the powdered lactose so the doses were indistinguishable in chocolate-brown masking capsules. Dosage was always 2 capsules daily, giving courses which consisted of 1.0 Gm., 0.5 Gm., and no cascara sagrada each day.

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Normal subjects were given 7 days of each preparation, while the constipated patients were given 14 days. The first day of each treatment period was omitted from the data analysis as representing possible overlap from the previous treatment. To prevent early defection of the constipated patients, their initial prescription was always an effective laxative. After 2 weeks on the standard cascara solution the actual experiment was begun with random administration of the three test materials. Since some of the patients might go through the interval between clinic visits without a bowel movement, it was necessary to allow the customary laxatives if several days passed without a bowel movement. When only active agents are compared, the practice of adding outside laxatives to the test program might be eliminated.

RESULTS

Fig. 2 presents a graphic summary of the responses in both normal and constipated patients. Inspection suggests that neither the number nor consistency of stool was altered by the "unknown" bran preparation, whereas the

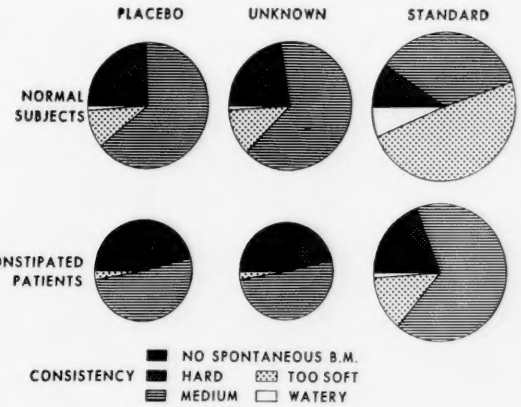

Fig. 2.—Summary of response to laxatives. The area of each circle is proportionate to the average daily frequency of bowel movements, while sections of the circle give the relative number of daily consistency judgments on each treatment.

standard laxative increased the number of evacuations and softened the consistency.

Consistency of stool is commonly analyzed by the assignment of plus values, from 1 to 4, to each category, a procedure which arbitrarily fixes the relationship between consistencies. In this study the ridit transformation was used to convert the attributes of consistency to numerical values according to the distribution of categories in the model population. Table I outlines the simple calculations, based on the placebo response in subjects with normal bowel habits. Taking cumulative percentage for the categories in an ascending scale, the conversion factor for each category is the center value in its band of percentage. These factors are substituted for the consistency categories of each day, and their average during the course of treatment provides a single numerical value for that treatment in each subject. Common statistical tests of significance can be applied as the next step. The ridit transformation is described in detail by Bross.[6]

TABLE I. CONVERSION OF CONSISTENCY CATEGORIES TO RIDIT SCALE
(Data From 40 Normal Subjects 6 Days on Placebo)

	NUMBER OF DAYS	CUMULATIVE PERCENTAGE	CONVERSION FACTOR
Took extra laxatives	0	0.0	0
No stool	16	6.6	0.033
Hard	35	21.2	0.140
Medium	156	86.2	0.538
Too Soft	30	98.8	0.927
Watery	3	100.0	0.996
Total	240		

Responses of normal subjects are summarized in Table II. From the analyses of variance (Snedecor[7]), it is clear that the method detects differences among the treatments. Paired analyses t tests (Snedecor[7]) gave no indication of differences between placebo and unknown, but P values were <0.01 for both number and consistency changes due to standard, 2 c.c. bitter cascara daily. Further properties of the ridit transformation may be illustrated with values from Table II. Consistency of the young adult population will be at the center point (the extra 0.003 of placebo comes from rounding), while other distributions give not only the relative consistency (the standard at 0.720 is toward the soft side of medium), but also the fractional odds that the particular treatment will be higher on the subjective scale. Thus there are about 3 out of 4 chances (0.720 is almost 0.75) that a subject will have softer stools on standard than on placebo (Bross[6]).

Normal variation in bowel habits may be noted in the placebo period, where 7 per cent of the days passed without a bowel movement. At some time during the 12 nonlaxative days (placebo and unknown), 47 per cent of the 40 normal subjects passed at least 1 day without elimination, several missed 2 or 3 days, one 5 days, and one a total of 6 days without evacuation.

Turning to the constipated patients, preliminary examination of data from 12 patients showed clear changes during the standard but only minor differences between the bran mixture and placebo. It was decided to emphasize any mild laxative action the bran mixture might possess. Accordingly the concentration was doubled so that, in the unknown course, dosage was equivalent to 6 cups of the bran beverage daily. Since the bran extract might act only after a period of cumulation, 1 or 2 weeks' pretreatment with bran preceded the 14-day test period.

TABLE II. COMPARISON OF LAXATIVE AGENTS
(40 Normal Subjects 6 Days on Each Agent)

	UNKNOWN-I	PLACEBO-II	STANDARD-III
No. of stools per day (±S.E.M.)	1.33 (±0.083)	1.28 (±0.074)	1.91 (±0.114)
Consistency on ridit scale	0.479 (±0.026)	0.503 (±0.025)	0.720 (±0.030)

Mean Square From Analysis of Variance

SOURCE OF VARIATION	FREQUENCY	CONSISTENCY
Between subjects	0.647	0.063
Treatments		
I-II	0.028	0.010
2III-(I+II)	9.010*	1.381*
Within groups		
within (I-II)	0.090	0.007
within 2III-(I+II)	0.259	0.018

*Significant at the $P = 0.01$ level.

Twenty patients completed the three test periods supplying all the data analyzed. They were about one-third of the 61 constipated candidates for the study. Another one-third of the candidates were satisfied with their self-administered program and could not be induced to attend clinic at 2-week intervals. The remaining patients were lost by intercurrent illness (5 patients), would not mark the report cards (7 patients), or would not maintain dosage, reducing medication when active and discontinuing when it appeared to be inactive (8 patients).

Table III summarizes the data from constipated patients, and analysis of variance is used to identify differences among treatments. The unknown bran mixture could not be distinguished from the placebo, either on the basis of frequency or consistency of stools. (Paired analysis t test gave P values >0.3 and >0.4, respectively.) On the other hand, compared to placebo, the cascara standard gave distinct improvement in both frequency ($P = 0.01$) and consistency ($P < 0.01$). It is to be noted that not every patient recorded better evacuation with cascara. In the 13 days of comparison, 1 patient reported 6 hard stools on

standard and 8 hard stools on placebo; another recorded 7 medium stools on both materials. The remaining 18 patients had more frequent bowel movements on standard, ranging from 1 to 62 stools more than on placebo. On the consistency scale, 4 patients had slightly softer stools on placebo than standard; 3 of these were not constipated in the physiologic sense, averaging 1.2 stools daily with consistency of 0.54 on placebo. The fourth was the patient mentioned above who had 2 less evacuations on cascara. At first he appeared to be resistant to cascara, but subsequent trials gave the typical increase in frequency and softening. His data led to the dilemma familiar to pharmacologic study on outpatients. No clue could be found to assign this anomalous result either to transient resistance of the gastrointestinal tract or to experimental defect such as deliberate evasion by the patient or error in recording code numbers.

TABLE III. COMPARISON OF LAXATIVE AGENTS 20 CONSTIPATED PATIENTS 13 DAYS ON EACH AGENT

	UNKNOWN-I	PLACEBO-II	STANDARD-III
No. of stools per day (±S.E.M.)	0.77 (±0.096)	0.85 (±0.095)	1.52 (±0.228)
Consistency on ridit scale	0.328 (±0.040)	0.335 (±0.034)	0.494 (±0.039)

Mean Squares From Analysis of Variance

SOURCE OF VARIATION	FREQUENCY	CONSISTENCY
Between subjects	0.611	0.059
Treatments		
I–II	0.202	0.000
2III-(I+II)	6.569*	0.343*
Within groups		
within (I-II)	0.056	0.005
within 2III-(I+II)	0.701	0.020

*Significant at the $P = 0.01$ level.

During their respective placebo trials, constipated patients reported a frequency of stool significantly lower than normal subjects ($P < 0.01$). There was overlap between the groups, with 2 of the 20 constipated patients ranking above the mean for the normal subjects. The size of the response to standard is not directly comparable, since the cascara dose was doubled for constipated patients, but their less impressive increase is compatible with the general theory that constipated subjects are less sensitive to laxation. Four cubic centimeters of cascara sagrada daily brought their average frequency of stool up to the range of untreated normal subjects.

Even on placebo, 4 of the 20 constipated patients met the common requirement of folklore, that of one stool each day. Fourteen met the criterion of effective laxation common to clinical trials in not resorting to extra laxatives

during the 2-week trial on placebo. A brief attempt was made to assess the effect of placebo by asking patients to record their stools without taking any medicine, either prescribed or self-administered. These attempts met anxious resistance, even from patients who did well on placebo, and when insisted on were defeated by broken appointments and failure to mark cards or to continue without help from familiar nostrums.

The consistency ratings between the groups should not be compared, since there are no data to validate criteria of judgment among various patients. Chronically constipated patients may well distinguish between hard stools and medium stools at an absolute level far removed from that of normal young adults. Consistency data are contrasted only in the same patient, an analysis requiring no assumption except that such subjective judgment does not show erratic distortion. Any systematic trend on time would be eliminated from the comparison by random sequence of presentation of the treatments. Incidentally, within each treatment period there was no evidence of cumulation or tolerance. In particular, during the bran mixture, the first week was identical with the third or fourth week of treatment.

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One question of special concern to methodology is whether the consistency judgments provide information in addition to that provided by frequency. Correlation coefficients between frequency and consistency were calculated for the treatment periods. In normal subjects they were close to zero for unknown and for placebo periods (+0.02 and +0.03); that is, frequent stools in the young adult are as likely to be hard as they are to be soft. On the other hand, the original data show a high relationship between frequency and consistency in constipated subjects. During placebo the correlation was +0.76 and during unknown it was +0.84. Part of this relationship is artifact introduced by the 0 movement point which is placed at the hard extreme of the consistency scale. For whatever reason, there was a clear distinction between people who consider their bowel function normal and those who consider themselves constipated. In the normal subject, frequency and consistency were unrelated; in the constipated patient, they were highly correlated.

When changes in each of the subjects from one treatment to another were considered, there was moderate correlation in all cases. The changes between the period of placebo and that of unknown for normals gave +0.46 and for constipated subjects +0.63. These represent ordinary day-by-day fluctuation rather than treatment effect, as can be seen in the breakdown of changes in the 40 normals. Compared to placebo, 11 subjects decreased in frequency and hardened in consistency on unknown, while 10 subjects both increased and softened. Only 6 of the 40 moved in one direction on one scale and in the opposite on the other, and none of these were large displacements. The changes induced by active laxation (placebo vs. cascara) showed a correlation of +0.53 in normals and +0.50 in constipated patients. These correlations seem low in view of the fact that three-fourths of both groups increased in frequency and also softened on standard. A scatter diagram indicated that the increase in frequency bore little relation to the degree of softening.

As a final step in exploring the sensitivity of the response, 12 of the constipated patients were placed on USP cascara sagrada capsules. Dosage-response curves are plotted in Fig. 3, showing that both frequency and consistency rose sharply between the low dose and placebo, but the increment of response was small when that dose was doubled. A paired t test comparison gave P values 0.05 and <0.01 for change in frequency and consistency from placebo to low dose, but the test between low and high dose failed to reach significance. The consistency leveled off, as if constipated patients reached their maximum effect well below that possible in normal subjects. This ceiling may be an artifact from the attitudes that constipated patients bring to the act of judging consistency.

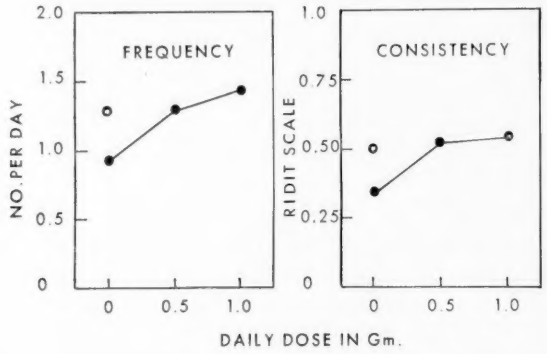

Fig. 3.—Dosage-response curves of powdered USP cascara sagrada in 12 constipated subjects. The open circles indicate results from placebo in normal subjects.

DISCUSSION

This presentation neither defends nor deplores the widespread use of laxatives by the public. Its concern is with methods for measuring the action of drugs in human patients. Laxatives are relevant only as a class of drugs sorely in need of the application of pharmacologic principles in their clinical trials. The "unknown" test preparation reported here, a beverage containing an extract of bran, was appropriate for this purpose. Though of little intrinsic interest, bran is associated in the public mind with regular bowel habits, and the beverage had collected testimonials describing a laxative effect. Evidence in the literature (Cowgill and Anderson[8]) indicates that the fiber content of bran accounts for its effect on stool.

Certain methodologic procedures and precautions are essential if answers in clinical pharmacology are to have any degree of permanence. The placebo effect, a shorthand way of saying that the patient's psyche induces responses to the doctor's interest and prescriptions, means that pharmacologic effects emerge only as the difference between two agents, the placebo and the unknown. No comparison between the treated and untreated states can isolate pharmacologic actions in patients.

The physician's psyche, too, may alter drug response by the unconscious attitudes imparted to the patient before the drug is taken and when the drug

effects are being assessed. The ideal solution is the "double-blind" test, in which the physician who administers the drug and the one who makes the judgments do not know which agent is being administered nor when agents are changed. Double-blind tests presuppose a team of physicians. As formulated below, it is not our concern to outline the best method, but rather the best method possible for wide use by individual physicians. The physician's attitude as he administers the drug does influence the actual effect (Shapiro and associates[9]), but even more distorting is the physician's attitude as he elicits the drug response from patients (Gold and others[10]). Interpersonal activity between doctor and patient when they review the interval and seek to make a critical judgment cannot fail to influence which events the patient remembers and the slant of his descriptions. The daily report card, which enables the patient to make all the judgments about drug responses without the physician's presence, removes the latter source of error though it clearly does not have the complete effectiveness of "double-blind" administration of the test materials. In our judgment the distorting factor will not be excessive in laxative testing and will enable a single physician to utilize the method by himself. Where the situation permits, complete double-blind testing offers theoretical advantage.

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The order of presentation of the test materials must be randomized to prevent systematic bias. For example, the placebo effect may be larger with the first administration of a new preparation, so if one agent were always given first a natural bias might develop in its favor. Finally, the sensitivity of the method of study must be calibrated by including a drug of known activity in the experimental plan. In this case the response to cascara sagrada proved that laxative effects can, in fact, be isolated by this method of study in these particular subjects. The additional effort required to measure consistency was justified, for its changes correlated with those of frequency only at the +0.5 level. Furthermore, a new laxative might change one response and not the other and thus need restriction in therapeutic application.

With powerful analgesics or the newer antibiotics, alteration of bowel habit is a familiar side effect. Important medical indications for a drug tend to discount the presence of such undesirable actions. But they need not be tolerated from new chemicals which come into the food habits of the nation on a casual basis. The method presented in this paper would offer convenient resolution for questions of this sort. For example, the artificial sweetener, cyclamate sodium, in dosage of 5 Gm. a day for 7½ months, was determined to soften the stool of human patients (Schoenberger and colleagues[11]).

The major purpose of our emphasis on method lies in another direction. In the case of laxatives, as in most other areas of therapeutics, the shelves of pharmaceutical companies are filled with bottles of organic compounds that have passed through animal screening tests and are favorable candidates for clinical trial. At this point two barriers are encountered on the logical path to therapeutic progress. First, the clinical trial in its common form is expensive. Economic facts dictate that patent rights have at least as much voice as favorable pharmacologic properties in determining which compounds come to trial. The second barrier is erected in the nature of the clinical trial. It rarely offers evi-

dence to orient the new agent toward its most desirable role in the gradually evolving structure of therapeutics. There is not sufficient time and manpower for enough of the ordinary kinds of trials to gain even a clinical impression about most of the materials which show promise in animal testing.

The development of methods for use by practicing physicians is the only feasible solution to this impasse. Methods in clinical pharmacology cannot require elaborate equipment nor disturb the ordinary patient-physician relationship. Answers of known reliability must be guaranteed by the experimental design. Physicians with a mild inclination toward research could apply such methods within the structure of their own practice, break the "bottle jam" on the pharmaceutical shelves, return most of these unknown compounds firmly and securely to laboratory limbo, and retain the few that offer particular promise.

In line with the current trend, pharmaceutical promotion introducing new agents which increase and soften evacuation has recently laid special emphasis on the position that they are not laxatives. Without challenging definitions, it is appropriate to point out that much of the promotional and scientific effort is thus committed to formulating theoretical concepts. Such reversal of the meaning of words may indeed be sound business policy. Nevertheless the cause of therapeutics would be better served by quantitative measurement of the effectiveness of these agents as compared to laxatives in long use and known to every hospital intern.

In the episodic papers that often support the introduction of new laxatives, a common fallacy may occur which can be illustrated by data from this study. A series of subjects are collected who say they are constipated. Their familiar program of laxation is stopped and the new agent substituted. Examination of Table III shows that during the substitution of a new agent, the inert placebo, an average of almost one bowel movement a day was reported by patients who claimed to be constipated. Fourteen of the 20 patients were able to go through the entire 2-week period on placebo without resorting to laxatives. At least, in our clinics, constipated persons are those who think they are not having enough bowel movements.

SUMMARY

1. A method is described for detecting laxative action in normal human subjects and for measuring the potency of laxative agents in constipated patients.

2. Since the subjects record all observations on a daily report card, one physician can apply the method, retaining most of the advantages of the "double-blind" test. Dosage is constant over 1- or 2-week intervals.

3. Both frequency and consistency of stool are measured, for the correlation between these two responses is only +0.5. The subjective categorical judgments of consistency are converted to a single numerical value by the ridit transformation.

4. The laxative potency of an unknown agent emerges from the comparison of its results with those of placebo. The sensitivity of the method is calibrated by a standard laxative, USP fluid extract cascara sagrada in daily doses of 2 c.c. to normal subjects and 4 c.c. to constipated patients.

5. With this method the unknown preparation, a beverage containing an extract of bran, was not distinguished from placebo by a group of 40 normal subjects nor by a group of 20 constipated patients.

6. Dosage-response curves in constipated patients indicate that greatest sensitivity to dosage change lies below 0.5 Gm. daily of powdered USP cascara sagrada.

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Review

DIABETES MELLITUS AND PULMONARY TUBERCULOSIS

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FOR many years the association of diabetes and tuberculosis has been recognized.[1-6] The specialist in metabolic diseases has been aware of occasional dramatic situations in which a diabetic has inexplicably become difficult to control and subsequent developments have led to the diagnosis of intercurrent tuberculosis. The chest specialist has always had to manage diabetes mellitus in a significant percentage of his tuberculous patients.

Diabetes has had other notable disease interrelationships, particularly staphylococcal infections and vascular diseases. Even in the years when there was a vogue among internists to mimic Procrustes and tailor all signs and symptoms to fit one diagnosis, diabetes was an exception to the rule. Maher and associates[7] recently pointed out the increasing need for critical and studious evaluation of diabetics, not only in regard to their diabetes, but also in regard to secondary disease entities.

The rapid increase in the older segments of our population continues and, with it, an increase in the diabetic population. One wonders, in view of the diabetogenic effect of cortisone, whether the increasing stresses of modern life may be converting to overt diabetes older persons with diabetic tendencies who, under less stressful conditions of life, might never have developed frank diabetes.[8-14]

Meanwhile, tuberculosis mortality rates are dropping. Morbidity should also diminish. Tuberculosis used to be considered a disease of youth. Today tuberculosis wards are largely filled with young Negro females and elderly white men. The latter largely represent those who, during youth, contracted tuberculosis and in whom the disease underwent arrest but who, under the unfavorable conditions of older age, have relapsed. These older tuberculosis patients constitute the major reservoirs of tuberculous infection in our midst, a particular menace to susceptible groups like silicotics and diabetics.

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The availability of newer therapeutic agents permits diabetics and tuberculosis patients to survive despite coma, meningitis, and other major formerly fatal complications. It is, therefore, important to know the changing patterns in both diseases.

Before discussing the association of any two diseases, consideration must be given to criteria for their diagnosis, the degree to which the two diseases are known and recognized in the population, and the prevalence of each disease in a characteristic sample of patients with the other disease.

DIABETES MELLITUS

Diagnosis.—Diabetes mellitus is characterized classically by glycosuria, hyperglycemia, and lowered glucose tolerance. Duncan[15] in his text, *Diseases of Metabolism*, states that the diagnosis of diabetes mellitus is made by the appropriate consideration of symptoms, family and past history, physical findings, and, "much more sensitive," the confirmatory laboratory data. The latter are glycosuria with concomitant hyperglycemia on an unrestricted diet, a fasting venous blood sugar value above 120 mg. per 100 c.c. and postprandial values in excess of 160 mg. per 100 c.c. or, if capillary blood is used, a fasting sugar above 120 mg. or a postprandial value above 190 mg. per 100 c.c. The diagnosis should not be made on the basis of one blood sugar determination since transitory hyperglycemia and glycosuria are not uncommon in head injuries, intracranial infection, thyrotoxicosis, hyperpituitarism, conditions affecting the adrenal glands, emotional disturbances, diseases of the liver, during anesthesia, asphyxia, and chemical poisonings. A blood sugar of over 160 mg. per 100 c.c. 1 or 2 hours after a meal containing 100 Gm. of carbohydrate indicates diabetes provided no complications are present which might alter carbohydrate tolerance. The standard glucose tolerance test is an important diagnostic aid. For valid conclusions, at least 300 Gm. of carbohydrate per day for 3 days should have been taken prior to the test. Two values are of outstanding importance—the fasting blood sugar value the day of the test and the blood sugar value 2 hours after the ingestion of 100 Gm. of glucose (or 1.75 Gm. per kg. of body weight in the case of a child). Fasting blood sugar values in excess of 130 mg. indicate diabetes unless proved otherwise. The normal individual is able to restore the blood sugar to 120 mg. or lower 2 hours after glucose ingestion. Duncan[15] gives little heed to the peak value. The fasting blood sugar may be normal in diabetics. The most important value is that obtained at the end of 2 hours. Every diabetic patient, when suitably studied, will exhibit an elevated and prolonged glucose tolerance curve, but every high and prolonged curve is not indicative of diabetes.

In Luken's *Medical Uses of Cortisone*, published in 1954, Thorn and his group,[16] discussing the pharmacologic aspects of adrenocortical hormones in man, state that "patients who exhibit a diabetic response to corticotropin or steroid therapy may justifiably be considered latent cases of diabetes mellitus." They suggest that the use of these substances be investigated more thoroughly as diagnostic aids in the detection of latent diabetes mellitus. Conn and Fajans[12] used a cortisone-modified glucose tolerance test to bring to the surface the subclinical defect in carbohydrate metabolism. They found that 24 per cent of nondiabetic relatives of diabetics responded to this test in a specific manner.

Types of Diabetes.—For many years it has been apparent that the mild diabetes which, for the most part, has its gradual onset in obese persons beyond the middle years of life is a different disease than the severe diabetes of acute onset which occurs in thin children and young adults. Falta and Boller in 1931,[17] Falta in 1936,[18] Himsworth and Kerr,[19] Himsworth in 1949,[20] Harris in 1949,[21] and Bornstein and Lawrence[22] are among investigators who have written on this subject. Draper and co-workers,[23] in 1944, published a paper on 225 diabetics studied by anthropometric methods and somatotypings. They differentiated two morphologic types—a more linear type with generally severe diabetes sensitive to insulin and developing acidosis with poor control, and a heavier, more rounded type with less severe diabetes tending toward insulin resistance but having little tendency to ketosis or hypoglycemia. Lister and associates,[24] in a study published in 1951 on 100 patients attending the Royal Free Hospital Diabetic Clinic—a random sample with willingness to cooperate being the only selective factor, found a remarkable degree of accord between their work and that of Draper's group.[23] They postulated the actual insulin sensitivity of a patient as a fundamental constitutional characteristic. In 1955, Lister and Tanner[25] studied a group of 155 diabetic clinic patients and noted that both men and women whose diabetes was of gradual onset were more endomorphic and less ectomorphic than those whose diabetes had been of acute onset. Lawrence,[26] in 1951, classified human diabetics into those deficient in insulin and those not deficient in insulin. He divided the latter into the lipotrophic and the lipoplethoric. He ascribed the great increase in female diabetics over the past twenty-five years to this type and, not believing that inborn genetic types have changed, he ascribed the increase in obese female diabetics to abundance of food. Murray and Wang[27] studied 1,000 patients who had attended the Diabetic Clinic of Victoria Infirmary at Glasgow for more than one year. They reported that only 17.5 per cent of their obese diabetics required insulin while 92.0 per cent of their nonobese patients required insulin. Sheldon,[28] in the introduction to his *Atlas of Men*, pointed out a growing faith in the proposition that structure and behavior are continuously related. He conceived of the somatotype as a trajectory or pathway along which the living organism is destined to travel under average conditions of nutrition in the absence of grossly disturbing pathology.

These basic differences in types of diabetes must be considered in relation to tuberculosis among diabetics.

Mass Methods for the Detection of Diabetes.—Diabetes detected by physicians in their offices and in hospital clinics is probably limited to severe diabetes and to a small proportion of mild diabetes. There is real need for diabetes detection on an expanded scale. Among the mass case-finding studies reported have been those by Tiber and Kopetsky in 1941,[29] Gates in 1942,[30] Blotner and associates in 1943,[31] Spellberg and Leff in 1945,[32] Blotner in 1946,[33] and Wilkerson and Krall in 1947.[34] Since the American Diabetes Association sponsored the first Diabetic Detection Week in 1948, this annual November project has been increasingly popular. As with all survey methods, the yield is highest in selected population segments—those with a family history of diabetes, the obese, and older females. However, in view of the more serious nature of juvenile

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diabetes, it appears important that pilot studies in diabetes detection be conducted among children. Sharkey and his co-workers[35] found, among 38,528 Dayton school children, that 0.05 per cent had proved previously unsuspected juvenile diabetes even though the follow-up on those with positive survey findings had been poor.

All authors on the subject of diabetes detection are agreed that diabetes mellitus cannot be ruled out by a single sugar-free urine nor a single fasting blood sugar at or below 120 mg. per 100 ml. Harting and Glenn,[36] using both urine and nonfasting capillary blood studies in a diabetic detection study of 3,186 Brookline, Massachusetts, citizens over the age of 25, found 71 previously unknown diabetics. If only those with more than a trace of glycosuria had been re-examined, only 40 of the 71 unknown cases of diabetes would have been found. If only those with blood sugar levels higher than the figures set for screening purposes had been re-examined, only 58 of the 71 new diabetics would have been found. They concluded that blood sugar screening has greater efficiency than urine screening for diabetes detection. Petrie and associates[37] agreed with this conclusion and emphasized the inadequacy of fasting blood sugars for case-finding purposes. Chesrow and Bleyer[38] pointed out that blood sugar rather than urine sugar screening tests are especially important in the aged since elderly diabetics tend to have a high renal threshold for glucose.

Spellberg and Leff[32] studied diabetes mellitus and glycosuria among 32,033 consecutive selectees at the New Orleans Induction Center. In mild, previously undetected, asymptomatic diabetics, the glucose tolerance test was their sole criterion. Yet the boundary between normal and abnormal tolerance curves is not sharp, varies with different authorities, and is beset with pitfalls. Reinberg with others[39] felt that a single blood sugar test 2 hours after 50 mg. of dextrose was superior as a screening technique to a single uncontrolled blood sugar or urine sugar. A single abnormal glucose tolerance curve should not be used to diagnose diabetes mellitus any more than should abnormal findings in a single urine or blood test. An abnormal diet prior to the test may produce an abnormal curve.

Getting's group,[40] reporting in 1952, evaluated a method of self-testing urine for glycosuria. Their primary purpose was to study a community's ability to perform a specific procedure. Following suitable preliminary publicity, 3,252 self-testing kits were made available without cost at Gloucester, Massachusetts, pharmacies. These were all picked up within 4 days but, of the 2,911 who returned their questionnaries, only 1,430 had performed the tests.

Harwood[41] conducted a follow-up study three months after a New England "Diabetic Fair" in which urines and bloods had been examined. Questionnaries were sent to 316 of the persons with positive tests. Of the 255 questionnaries returned, 179, or 70 per cent, had consulted physicians. In 50 instances, a diagnosis of diabetes had been made. In 97 cases the physician had stated that diabetes was not present. In 26 instances no definite statement had been made to the patient.

Follow-up techniques are an essential part of detection. There is no great practical virtue in knowing the number of persons in a given group who have

glycosuria and/or hyperglycemia if such individuals do not report for diagnosis or if the subsequent diagnoses are not based on adequate studies.[42]

In general, accepted mass techniques for detecting diabetes are based on screening histories and nonfasting urine and blood studies followed by diagnostic glucose tolerance tests. As in all survey work, the screening levels should be set too low rather than too high in an effort to funnel all suspects to the clinician for diagnostic studies.

Prevalence of Diabetes.—The prevalence of diabetes mellitus is not known. The first valid estimate was 660,000 for known United States diabetics based on the National Health Survey[43,44] 1935-1936 house-to-house canvass of 800,000 families including 2,800,000 persons. Spiegelman and Marks,[45] using the National Health Survey data, estimated diabetes prevalence to be 3.67 diabetics per 1,000 urban dwellers—2.73 for males and 4.53 for females. There was no sex difference under the age of 25, but, from then on, females had increasingly higher rates until, between the ages of 45 and 64, the female prevalence rate was almost twice that for males.

After the age of 65, the sex differential diminished. Monroe,[46] in a study of 7,941 individuals over 61 years of age, gave the following figures for the prevalence of diabetes: those studied between 1913 to 1923, 7.8 per cent; 1923 to 1933, 9.7 per cent; and 1933 to 1943, 10.9 per cent. By age groups, the figures were: 61 to 70, 10.7 per cent; 71 to 80, 8.4 per cent; 81 and over, 3.7 per cent. Apparently, those who live longer than the Biblical allotment of threescore years and ten are a special breed of hardy individuals in regard to diabetes as in relation to most other diseases.

An increase in diabetes is inevitable because of better case-finding, higher living standards with increased food consumption, decreased physical exertion associated with increased mechanization, the general increase in longevity, and the increased duration of the diabetic's life through better therapy of diabetes and its complications. Spiegelman and Marks[45] postulated that, between 1940 and 1950, the diabetic population would increase 18 per cent compared with an increase of 9 per cent in the general population. Wilkerson and Krall[34] estimated that there would be a million known diabetics by 1950. Actually, the April, 1956, Summary of Health and Vital Statistics[47] estimated two million United States diabetics, one million known and one million unknown. Prevalence figures obtained by surveys vary from 0.3 per cent reported by Spellberg and Leff[32] for their already screened selectees, through Petrie and his colleagues'[37] figure of 0.4 per cent for 248,176 Georgia citizens to Ford's[48] 4.1 per cent of 736 Jacksonville relatives of diabetics. Blotner and Marble[49] believe there are three unknown diabetics to every known case.

TUBERCULOSIS

Diagnosis.—Early tuberculosis may be asymptomatic or there may be vague complaints of fatigue, anorexia, low-grade fever, or slight cough. On the other hand, hemoptysis may be the first symptom. Acute pleuritic pain, high fever, sweats, rapid weight loss, and racking cough are manifestations of advanced disease.

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Changes in the roentgenogram may precede symptoms. For that reason, periodic chest x-rays are advisable for all adults. Serial films are always more helpful than single roentgenograms. No person should be told he has an old inactive tuberculosis on the basis of a single x-ray. Where radiologic findings seem important and all clinical methods fail to yield a diagnosis, there is an increasing tendency to resort to biopsy of the lung or resection of the involved segment.

Judgment is indicated in the interpretation of physical signs. The absence of abnormal findings cannot rule out tuberculosis. The presence of abnormal signs may not necessarily mean tuberculous activity. While there is more tuberculosis found among those underweight than among those overweight, individual tuberculous patients may be obese or may gain weight while the disease progresses. The erythrocyte sedimentation rate may be elevated in active tuberculosis, but a normal sedimentation rate is not necessarily associated with stability.

The diagnosis of active pulmonary tuberculosis is based on adequate bacteriologic or tissue proof. When sputum is available, several specimens should be examined by smear and confirmed by culture. One positive sputum report may be erroneous. In the absence of sputum, gastric washing cultures are indicated. Smears of gastric contents should not be examined because of the risk of false positives due to the presence of nontuberculous acid-fast bacilli. If bronchoscopy is indicated clinically, bronchial secretions rather than gastric washings should be studied. Bronchial secretions have the virtue of being aspirated directly from the suspected portion of the bronchial tree.

In the absence of sputum, the tuberculin test is of special importance since, for all practical purposes, except for the first three to seven weeks after infection or the presence of critical illness, failure to react to intracutaneous tuberculin rules out active tuberculosis. Recent tuberculin conversion is of great value. Converters may be carefully followed by clinical and radiologic means. If illness or x-ray changes occur, converters may be treated as tuberculous with confidence. There is even a trend, still controversial, toward treatment of tuberculin converters in the absence of clinical illness.

Unexplained pleural effusion should be considered tuberculous until proved otherwise. Even in older aged groups, primary tuberculous effusions are encountered, probably because of the increased age at which infection now takes place. The technique of pleural biopsy has been perfected and is being used increasingly in equivocal cases.

A history of intimate contact with a tuberculous patient, recent delivery, previous pleural effusion, diabetes, silicosis, or cortisone therapy are indications for heightened suspicion of tuberculosis.

Mass Methods for the Detection of Tuberculosis.—Mass chest x-rays[50] for the civilian population became popular in the United States immediately after World War II. Millions of miniature photofluorograms have been exposed since then and the tuberculosis so detected is preponderantly minimal in stage in contrast to the advanced stage of disease that has characterized sanatorium admissions.[51] Either gross over-reading[51,52] or dual reading by skilled physicians[53-55] is advisable

for survey films in order that all suspicious lesions be screened out. The technique is particularly effective if a brief screening history[56] is taken at the time of the chest x-ray to guard against false reassurance. However, so far as tuberculosis is concerned, chest roentgenograms are apt to reveal lesions before symptoms are present and are, therefore, helpful tools in case-finding. As in all surveys, the highest yields will be obtained in selected population segments—older individuals,[57] those below standard weight, silicotics, diabetics,[58] those with a history of recent delivery, pleurisy, "viral pneumonia," or from lower socioeconomic groups.

Another approach to the detection of tuberculosis is through tuberculin testing in which there is a renaissance of interest. The tuberculin test gauges not the presence of active tuberculosis but the presence of tuberculous infection. Allergy to tuberculin develops three to seven weeks after infection and usually remains throughout the balance of life. For all practical purposes, a positive reaction to tuberculin means the presence of viable tubercle bacilli within the body. It is among these "positive" individuals that clinical tuberculosis will be found or may develop. Yet, in the absence of illness or detectable chest x-ray abnormalities, a positive tuberculin test signifies the presence of some resistance to tuberculosis since infection has been encountered and handled well. Those who react to tuberculin should certainly be checked by x-ray annually or semiannually, depending on circumstances such as stress, complicating disease, contact with the original source of infection, etc.

The intradermal tuberculin test is the most reliable test. In areas of low tuberculosis mortality and morbidity, the intermediate strengths of tuberculin may be used as the first test dose—0.0001 mg. P.P.D. or 0.1 mg. O.T. However, in areas where high infection rates may be anticipated, as in the large eastern cities, to avoid troublesome reactions, it is wiser to use two test doses—the first 0.00002 mg. P.P.D. or 0.01 mg. O.T., and, if there has been no reaction to this dose, then 0.0001 mg. P.P.D. or 0.1 mg. O.T. Furcolow and associates[59] demonstrated that the old full second strength tuberculins elicited some nonspecific reactions so these stronger dosages are not extensively used. Patch tests yield both false positives and false negatives and, therefore, are not appropriate for precise work.

It is important that fresh tuberculin testing material be used, that technique be meticulous, and that interpretation of the results be by experienced nurses or physicians. The test is read 48 to 72 hours after injection. An area of at least 5 mm. of induration is necessary for a positive test. The test results should be recorded as "—— mm." since there is a correlation between increasing size of reaction and probability of having or developing active tuberculosis.[59a]

Tuberculin screening, in addition to its usefulness as an epidemiologic tool, may well be used for groups with special risks—diabetics, silicotics, prenatal patients, and school children in areas of high tuberculosis morbidity. Knowledge that such individuals do not react to tuberculin is reassuring. Periodic tuberculin testing reveals the time of conversion so that careful search for clinical illness can be made at frequent intervals.

Prevalence of Tuberculosis.—The prevalence of significant clinical tuberculosis is unknown.

For many years the disease has been followed by decreasing mortality rates, and pride in the drop from 194.4 per 100,000 in 1900, to 9.0 per 100,000 in 1955 is justifiable.

As pointed out by Smith[60] in his 1951 presidential address to the National Tuberculosis Association, tuberculosis death rates began falling before Koch discovered the tubercle bacillus. Before the advent of streptomycin, the diminishing mortality rates were partly due to factors involved in genetic selection and survival of resistant persons. Undoubtedly, the antimicrobial era will alter this pattern. Improved nutrition associated with better standards of living, knowledge of the infectious nature of tuberculosis, adequacy of beds for isolation and therapy, and the great educational campaigns launched and maintained by the powerful network of local affiliates of the National Tuberculosis Association have all been factors in lowering mortality from tuberculosis.

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The tuberculosis problem is concentrated in the lower socioeconomic groups where poverty precludes adequate diet, crowding means inadequate rest and large dosage of infection. Overwork, with its undue physical stress, and worry, with its undue emotional stress, often add to this already fertile background the final factors involved in succumbing to the infection. Occasionally, active tuberculosis occurs at higher socioeconomic levels, either associated with massive exposure—as in nurses or physicians, with excessive stress—as in harried executives or popular debutantes, or in special disease situations—as in diabetes, after cortisone therapy without antimicrobial coverage for apparently stable tuberculosis, etc.

Without accurate morbidity data, it is impossible to gauge tuberculosis prevalence. The closure of hundreds of sanatorium beds may be more a reflection of the increased number of patients being treated in their homes than of decreased need. It may require years to gauge the ultimate wisdom of the current trend of treating tuberculosis in the home where isolation techniques are so frequently misunderstood or disregarded.

Tuberculosis prevalence is often estimated from the number of newly reported cases of tuberculosis, or from tuberculosis deaths. Edwards and Drolet[61] first pointed out the discrepancies between tuberculosis death rates and morbidity. For a time, newly reported cases increased as death rates continued to fall. Probably this was due to increased case-finding efforts. In Philadelphia newly reported cases decreased between 1950 when the rate was 136.7 per 100,000 to 1953 when the rate was 103.8 per 100,000. However, the rate rose in 1954 and again in 1955 to 125.8 per 100,000.

Prevalence of "survey tuberculosis" varies with the philosophy of the survey readers. In Philadelphia gross overreading has always been used to screen out all those who could conceivably have tuberculosis. Prevalence figures have ranged between 2 and 3 per cent since 1947. For the United States as a whole, figures for mass surveys average 1.5 per cent.

Few data are available in regard to proved active tuberculosis detected by survey methods. The Philadelphia Tuberculosis and Health Association,[62] in analyzing follow-up on 71,528 persons surveyed October, 1954 to September, 1955, found 109, or 1.5 per thousand, to have been diagnosed and reported to the Department of Public Health as cases of active tuberculosis.

The level of tuberculin sensitivity is probably the most reliable index of the tuberculosis problem. So far as prevalence of tuberculin reactors is concerned, our information is spotty. Teague[63] found, among Philadelphia school children tested in 1948, 4.2 per cent reactors at the age of 6 compared to 16.4 per cent at the age of 16. The American Student Health Association[64] reported that, in 1947, 105,633 students tested in 91 colleges yielded 19 per cent reactors. The prevalence of reactors was 22.6 per cent among males and 9.4 per cent among females. Edwards and co-workers,[65] in 1948, found 12.6 per cent tuberculin reactors among 12,803 student nurses before contact with patients. No figures are available for the tuberculin status of large groups of adults, but, if the conservative over-all figure of 10 per cent tuberculin reactors be multiplied by the current United States population figure of 170 million, 17 million United States citizens have been infected by the tubercle bacillus. With the chronic and relapsing nature of tuberculosis, this core of tuberculin reactors should receive special attention.

TUBERCULOSIS AMONG DIABETICS

Prevalence.—While it is generally accepted that tuberculosis is more prevalent among diabetics than among nondiabetics, it is extremely difficult to compare reported prevalence figures. Joelson and Dolger[66] and King[67] emphasize this problem. Basic variations in source of diabetics—whether outpatient clinic, private physician ambulatory, hospital admission or autopsy material; in age, race, and sex, weight, duration and severity of diabetes, age at onset of diabetes, in geographic area, in diagnostic criteria, in adequacy of sample size, etc., are all involved. As far back as A.D. 600 the association of the two diseases was noted by Ayur Veda of Susruta.[68] In this country, Sosman and Steidl,[69] reporting in 1927, found that, among 1,074 diabetics admitted to Peter Bent Brigham Hospital, 3.0 per cent had a clinical diagnosis of tuberculosis. Fitz,[70] in 1930, felt that, of the three major complications of diabetes—acidosis, gangrene, and infection—infection in the form of pulmonary tuberculosis was, by all odds, the most serious. He reported that, of 1,529 diabetics attending the Peter Bent Brigham Outpatient Department, 35 had or developed active pulmonary tuberculosis. He reasoned that, adding to his own series Joslin's[71] (1928) reported 43 cases among 3,000 diabetics and Wilder and Adam's[72] (1929) reported 10 cases among 1,000 diabetics, there were 88 cases of tuberculosis among 5,500 diabetics, a tuberculosis prevalence of 1.6 per cent. Considering more than one million United States diabetics, one could estimate that 16,000 diabetics have active tuberculosis.

TABLE I*

AUTHOR	YEAR	NO. DIABETICS	NO. TUBERCULOSIS CASES	PER CENT TUBERCULOSIS
Golden[74]	1927	1091	51	5.0
Joslin[71]	1928	3000	43	1.4
Wilder and Adams[72]	1939	1000	10	1.0
Fitz[70]	1930	1529	35	2.3
Wendt and Peck[75]	1931	1073	42	4.1
Murphy and Moxon[76]	1931	827	40	4.8

*Banyai.[73]

Banyai,[73] in 1931, collected a larger series of 8,520 diabetics and calculated the tuberculosis prevalence to be 2.6 per cent.

Root's[77] 1934 study was the most important paper on the subject for some years. Among 1,659 diabetics studied between 1927 and 1930, he found that the prevalence of tuberculosis was 2.8 per cent. Gauld and Lyall,[78] in 1947, reported 17 cases of proven active tuberculosis among 717 diabetics treated between 1932 and 1946, a prevalence of 2.4 per cent. Joslin's group[79] reported 886 recognized cases of tuberculosis among 32,148 diabetics studied between 1898 and January, 1951, a prevalence of 2.8 per cent, the identical prevalence reported by Root almost twenty years earlier. Boucot and co-workers,[58] in a chest x-ray survey conducted in 1946 on 3,106 Philadelphia diabetics from 22 hospital clinics and 94 private physicians, reported a prevalence of 8.4 per cent, twice the figure for a group of 70,767 apparently healthy industrial workers adjusted to comparable age, race, and sex. The prevalence of "active survey tuberculosis" was 2.6 per cent.

Apparently the prevalence of clinically active tuberculosis among diabetics ranges between 2 and 3 per cent and has not changed significantly over the past twenty-five years.

Streptomycin was discovered only in 1944. Prior to that, the prognosis of diabetics with tuberculosis was so poor that, for general purposes, morbidity and mortality rates could almost be interchanged. Beardwood,[80] in 1944, reported an extremely interesting study of Philadelphia death certificates for the years 1940, 1941, and 1942. Diabetes was mentioned on 2,499 certificates of which 53 were coroner's cases. Of the balance of 2,446 cases, questionnaires sent to physicians were answered by 72 per cent. Of these replies 1,579 contained sufficient data for analysis. One hundred eighty-eight diabetics had died of infection. Among these, 33 had died of tuberculosis, a prevalence of 2.1 per cent, a figure that supports the clinical findings described above.

By age: In the general population, tuberculosis increases with increasing age. Fitz[70] reported that tuberculosis was not often encountered among young diabetics but more among elderly diabetics. He reasoned that this was due to an increased opportunity for infection the longer the diabetics lived. Another explanation may be that, at the time of his study in 1930, the younger more severe diabetics had a higher mortality rate so they may have died of diabetes before they had an opportunity to develop tuberculosis. Among 140,000 Massachusetts children of elementary and high school age, tuberculosis was present in 0.12 per cent, while among 750 diabetic children of the same age, tuberculosis was present in 1.6 per cent or 10 times as many.[81] Boucot's group[58] found 5.3 per cent "active tuberculosis" among 430 diabetics under the age of 40 compared with 1.7 per cent among the 2,653 diabetics older than 40. If diabetes predisposes to tuberculosis, this situation is logical since older diabetics are milder diabetics.

By race: Joslin[79] states that the once-held concept that Negroes were almost immune to diabetes is false. He gives no actual figures for prevalence of diabetes among Negroes but quotes Metropolitan Life Insurance Company data on industrial policy-holders that, among males, Negro death rates from diabetes tend to be higher than white races up to the age of 45 with a reversal

of this situation beyond the age of 45. Among females, there was the same trend but the reversal occurred at the age of 65. Tuberculosis runs a more fulminating course in Negroes with a higher case fatality rate than among whites. This has resulted in a lower prevalence of tuberculosis among Negroes than among whites since the segment of chronic cases has been low. In the Philadelphia Diabetic Survey,[58] the tuberculosis prevalence was almost 10 per cent among the 2,245 whites diabetics contrasted with less than half that figure, 4.3 per cent, among the 861 Negro diabetics. This ratio is about the same as that found in other Philadelphia tuberculosis surveys adjusted to comparable age and sex. In 1946, the year of the Philadelphia Diabetic Survey, Philadelphia tuberculosis mortality rates were 33.9 per 100,000 for whites and 182.9 per 100,000 for Negroes. In 1955, the rates were 25.3 for white males and 4.6 for white females compared with 54.7 for nonwhite males and 36.7 for nonwhite females. Mortality figures for Negroes should continue to drop at a proportionately faster rate than among whites because the acute exudative tuberculosis characteristically encountered among them is the type of disease most amenable to antimicrobial therapy.

It seems particularly important to seek out tuberculosis among Negro diabetics because of their higher mortality rates both from diabetes and tuberculosis.

By sex.—In the general population, tuberculosis is more of a problem among men than among women—particularly among the lone unloved men of Skid Row. In the Philadelphia Diabetic Survey[58] there was twice as much tuberculosis among males as among females. This was true for active tuberculosis as well as for total survey tuberculosis.

Time Relationships Between Tuberculosis and Diabetes.—All writers agree that diabetes usually antedates the onset of tuberculosis. In a series of 349 cases of diabetes and tuberculosis treated at Sea View Hospital between March, 1934, and December, 1939, Mark and associates[82] report that, in 60 per cent, the diabetes preceded the tuberculosis while, in 17 per cent, the two diseases were found simultaneously. Of 117 diabetic tuberculous patients treated at Herman Kiefer Hospital between 1934 and 1939, McKean and his group[83] state that diabetes preceded tuberculosis in 48 per cent. Of 38 diabetic tuberculous patients at La Esperanza Sanatorium, Havana, studied between 1950 and 1952, Reaud[84] reports that about half had had diabetes for periods up to five years before admission.

Boucot[58] postulated that, if diabetes predisposes to tuberculosis, an increasing prevalence of tuberculosis should be observed with increasing durations of diabetes. In her study, this was the case only for younger diabetics. The tuberculosis prevalence for those under 40 was 5 per cent with diabetes of less than ten years' duration, compared to 17 per cent in those whose diabetes had been known for more than ten years. Among those over the age of 40, the tuberculosis prevalence was 8 per cent regardless of duration of diabetes. This may reflect the more serious nature of diabetes in younger persons and the possibility that the susceptibles among the older diabetics may have died before the survey.

Since diabetes so often precedes tuberculosis, it is advisable to ascertain the tuberculin status as soon as diabetes has been diagnosed. Diabetics who do

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not react to tuberculin should be retested semiannually. Those diabetics who react to tuberculin should not only themselves be x-rayed every six months or more often if respiratory infection or unexplained fever occurs, but members of their households should be x-rayed annually to make sure that there is no contact with open tuberculosis.

Severity of Diabetes.—If diabetes predisposes to tuberculosis, then the more severe the diabetes the higher should be the prevalence of tuberculosis. Himsworth[20] states that tuberculosis is a complication of severe rather than of mild diabetes. The simplest index of diabetic severity, according to Lukens and Dohan,[85] is insulin dosage. These authors classify diabetics as mild if no insulin is required, moderate if 1 to 40 units are needed, and severe if more than 40 units are used. Mark and associates[52] use less than 20 units of insulin to designate mild diabetes, 20 to 40 units moderately severe diabetes, and more than 40 units severe diabetes. Whatever the scale of insulin dosage used to gauge severity, the patient requiring more than 40 units of insulin is considered by most authors to be a severe diabetic.

The Philadelphia Diabetic Survey[58] studied the relationship between severity of diabetes and prevalence of active tuberculosis. There was no difference between diabetics not requiring insulin and those requiring less than 40 units of insulin, but about twice as much active tuberculosis was present in those requiring more than 40 units of insulin per day. This was more dramatic in the 416 diabetics younger than 40 years of age, among whom those on less than 40 units of insulin had 2.7 per cent active tuberculosis compared to 8.8 per cent for those requiring more than 40 units.

Control of Diabetes.—It is very difficult to evaluate control of diabetes. In a disease of such chronicity, control often waxes and wanes so that the state of control at the time of tuberculosis detection may be basically unrelated to the onset of the tuberculosis. Infection of any type tends to shift diabetes out of control so that the status of diabetics with active tuberculosis may not reflect the true relationship of control to the onset of the tuberculosis.

King,[67] in 1936, stated without citing any supporting statistics, that most tuberculous diabetics seem to be neglected diabetics and that the frequency of tuberculosis among diabetics is an index of the adequacy of diabetic control. On the other hand, Thosteson and Tibbitts[86] stated that most of their 294 tuberculous diabetics were admitted with diabetes in good to fair control. Coma is certainly the hallmark of the gravest lack of control. Root and Bloor,[87] in 1939, reported 17.8 per cent of their diabetics who had had coma developed pulmonary tuberculosis within 5 years after recovery from coma. Yet Wilder and Adams,[72] in 1940, wrote that only 1 of their 89 coma cases had tuberculosis either before or after one or more attacks of coma. They emphasized that the undernourished diabetic is predisposed to tuberculosis. Prehaps the state of nutrition in various series rather than the coma per se may be the explanation of the wide variation in reports as to the relationship of coma to tuberculosis. Roche and co-workers[88] found no correlation between the amount of glycosuria and the degree of tuberculosis in cortisone-treated and alloxan diabetic rats. In view of the emphasis in the literature on a relationship between diabetic

control and tuberculosis, Boucot's group[58] studied control on the basis of 5 recent blood sugars and coma history. They were unable to establish a relationship between these factors and tuberculosis. Some of their findings tend to support Wilder and Adams'[72] convictions in regard to nutrition. Standard weight rather than control seemed of importance, those below standard weight all having had more active tuberculosis regardless of the state of control. Efforts to maintain normal blood sugar values in the presence of symptoms due to tuberculosis may account for this anomalous situation or 5 recent blood sugar values may be unrelated to the status of the diabetic at the time of tuberculosis onset.

Jacobs and associates[89] discussing 55 diabetic tuberculosis patients, feel that lability of diabetes rather than control per se is the important factor. They may well be correct since younger diabetics, more "severe" by the criteria of insulin dosage, are usually more labile diabetics.

Standard Weight.—Boucot's group[58] found twice as much survey tuberculosis in those below standard weight as in those above standard weight. When only active tuberculosis was considered, the contrast was more marked, 4.5 per cent compared to 1.0 per cent. The underweight diabetics under 40 had 6.2 per cent active tuberculosis compared to 3.1 per cent in the young overweight group. For those over 40 the figures were 3.9 per cent for the underweights compared to 0.7 per cent for the overweights. Thus, at all ages, thinness was associated with more tuberculosis and a higher percentage of active tuberculosis. The more severe the diabetes, the more impressive was the effect of underweight. Since accepted diabetic therapy emphasizes the desirability of reducing diabetics to or slightly below standard weight, the Philadelphia group felt it worth while to emphasize the increased prevalence of tuberculosis among underweight diabetics.

Duration of Diabetes.—The prognosis for diabetic tuberculosis patients was grave before the antimicrobial era so that severe diabetics who contracted tuberculosis may well have died before their diabetes was of long duration. Among 68 diabetic tuberculosis patients reported by Ferrara,[90] diabetes antedated the tuberculosis in 47, or 69 per cent. The duration of diabetes before tuberculosis was 0 to 2 years in 8 patients, 3 to 5 years in 15 patients, 6 to 10 years in 15, and more than 11 years in 9 patients. Thosteson and Tibbitts[86] reported that tuberculosis antedated diabetes in only 10 per cent of 294 diabetic tuberculosis patients discharged from Herman Kiefer Hospital from 1940 to 1952. One quarter of those with moderately and far-advanced tuberculosis had had diabetes for 10 to 14 years.

History of Contact With Tuberculosis.—No data are available on tuberculosis according to history of contact among large groups of nondiabetics but Boucot and others[58] found almost twice as much tuberculosis among the 298 diabetics with a history of contact with tuberculosis as among the 2,620 without a known contact. This relationship held when only active tuberculosis was considered. Therefore, it seems that a careful investigation of tuberculosis contact is especially important in diabetic history-taking.

There are considerable data on history of contact in tuberculous diabetics. Fitz,[70] in his series of 35 patients, and Root and Bloor,[87] in their series of 364

patients, elicited a history of contact in about one-third. Wiener and Kavee[91] reported 21 per cent of 218 tuberculous diabetics with a history of contact while the Philadelphia group[58] found a history of contact in only 13 per cent of their cases. One would anticipate fewer diabetic tuberculosis patients with a history of contact since greater susceptibility might well allow diabetics to become infected on the basis of more casual contact.

History of Pleurisy.—In the Philadelphia Survey, the prevalence of 4.2 per cent active tuberculosis among the 457 diabetics with a history of pleurisy was twice the figure for the 2,451 diabetics without such a history. This is in keeping with the time-honored adage that pleural effusions should be considered tuberculous unless proved otherwise.

History of Diabetic Complications.—The Philadelphia Survey[58] revealed no relationship between tuberculosis and history of gangrene and/or complications or of boils and/or carbuncles. Possibly, the lack of correlation may be related to nutritional status, tuberculosis occurring more in thin diabetics while staphylococcal infections seem to occur more in overweight diabetics. There is an impression among metabolic specialists that pneumonia is no more prevalent among diabetics than among nondiabetics.[92] Root[77] reported only 73, or 0.5 per cent, pneumonias among 13,188 diabetic admissions to the New England Deaconess Hospital.

Geographic Considerations.—King[67] pointed out that rural areas usually have lower tuberculosis mortality and morbidity rates than do urban areas. One might, therefore, anticipate less tuberculosis among rural diabetics than among urban diabetics. However, diabetes in rural areas is usually not diagnosed as early as in urban areas and may not be as adequately treated. This may account for Murphy and Moxon's report[76] of 4.8 per cent tuberculosis among rural Wisconsin diabetics compared to 1.6 per cent tuberculosis reported among urban Wisconsin diabetics by Sevringhaus.[93]

DIABETES AMONG TUBERCULOSIS PATIENTS

Most authors believe that there is no more diabetes among tuberculous than among nontuberculous patients. Landis and associates,[94] in 1919, reported that, of 31,834 tuberculosis patients in 25 United States sanatoria, 101, or 0.3 per cent, had glycosuria and 51, or 0.16 per cent, had diabetes. This prevalence of 16 diabetics per thousand tuberculosis patients is half the conservative estimate given by Spiegelman and Marks[45] based on the 1935-1936 National Health Survey data. The difference in these figures may be due to the increase in diabetes between 1919 and 1935. Tompkins,[95] in 1929, reported 0.3 per cent diabetics among 4,500 tuberculosis admissions to the Oteen Veterans Administration Hospital. In 1931, Banyai[73] reported 0.6 per cent diabetes among 5,224 consecutive tuberculosis admissions to Muirdale Sanatorium beginning Jan. 1, 1923. In 1944, he and Cadden[96] reported that, on 5,575 subsequent new Muirdale admissions, the prevalence of diabetes was 1.6 per cent. The identical figure, 1.6 per cent, for diabetics among 15,361 tuberculosis admissions to Herman Kiefer Hospital was reported in 1941 by McKean and colleagues.[83] Rubin[97] states that, of 414 tuberculosis patients over the age of 50 admitted to Montefiore

Hospital between 1926 and 1932, there were 72 diabetics or 17 per cent. Montefiore has a high Jewish population which, with the older age of the patients in Rubin's study, probably accounts for this high prevalence of diabetes. Wiener and Kavee,[91] in 1936, found 6.5 per cent diabetes among Montefiore tuberculosis patients. Reaud[84] found 1 per cent diabetes among 3,850 patients with active tuberculosis at La Esperanza Tuberculosis Sanatorium in Havana between Jan. 1, 1950 and May 31, 1952. Ferrara[90] reported 2.1 per cent diabetes among 178 tuberculosis patients admitted to Uncas-on-Thames Tuberculosis Hospital from July 1, 1937, to July 1, 1950.

Stage of Tuberculosis.—Of Ferrara's[90] 68 diabetic tuberculosis patients, only one had minimal tuberculosis, 25 per cent had moderately advanced disease, and 75 per cent had far advanced tuberculosis. Banyai and Cadden[96] reported 2 per cent of 125 diabetic tuberculosis patients with minimal and 83 per cent with far advanced disease. Thosteson and Tibbits[86] report better but not much more encouraging figures for 294 diabetic tuberculosis patients (minimal 7 per cent, moderately advanced 28 per cent, far advanced 65 per cent). While Boucot and others[58] found 63 per cent minimal among 261 diabetics with survey tuberculosis, only 19 per cent were minimal of the 80 diabetics with active tuberculosis. Even so, this is superior to the findings in sanatorium series and bears testimony to the advisability of using chest x-ray survey techniques periodically for detecting tuberculosis among diabetics. Most surveys of general populations yield 70 per cent minimal tuberculosis.[98]

Nature of "Diabetic Tuberculosis".—While serial roentgenograms give evidence that healed, fibrotic tuberculosis may remain inactive after the onset of diabetes, tuberculosis occurring after the onset of diabetes is usually acute exudative in type[69,99,100] progressing rapidly to excavation and characterized, if untreated, by a toxic downhill course. Banyai and Cadden[96] reported cavities in 70 per cent of their 125 patients. Myers and McKean[101] noted that 90 per cent of their diabetic patients had cavitation. Thosteson and Tibbitts[86] stated that two-thirds of their mild diabetics and three-quarters of their severe diabetics had cavitation, and these authors felt that there was no predictable correlation between severity of diabetes and extent of tuberculosis. The same situation has been reported by Wiener and Kavee[91] and by Reaud.[84] Not one of Reaud's 38 patients was asymptomatic.

Hemoptysis is more frequent in diabetic patients than in nondiabetic patients with tuberculosis.[102] Fishberg[103] states that 60 per cent of diabetic tuberculosis patients reported hemoptysis compared with 43 per cent of nondiabetics. Reaud[84] reported 10 of 38 diabetic tuberculosis patients had hemoptysis. Wiener and Kavee[91] reported fatal hemorrhage in 13 per cent of 130 diabetic tuberculosis patients dying at Montefiore compared with 6.8 per cent of tuberculosis deaths in nondiabetics. Is this due to the increased capillary fragility in diabetics, the cause of which is obscure?[104]

Fibrous adhesions are less common among diabetic tuberculosis patients, another shortcoming in their defense against the spread of tuberculosis and a probable factor in a tendency toward more pleural effusion. Two of McKean and colleagues'[83] 117 diabetic patients had pleural effusion. Four of Boucot's[58]

80 active cases had pleural or pericardial effusion. In the days when pneumothorax was popular, pneumonolysis was required less frequently among diabetics. Healing seems slower in keeping with the easy bruising and slow healing characteristic of diabetics.

So far as site of tuberculosis is concerned, the old concept of more mid-lung and basal tuberculosis among diabetics was not supported by the findings in the Philadelphia Diabetic Survey.[58] Age rather than diabetes seemed to explain the apparent predominance of mid-lung and basal disease.

Therapy.—The acute nature of "diabetic tuberculosis" makes it particularly vulnerable to modern antimicrobial drugs—streptomycin (SM), para-aminosalicylic acid (PAS), and isoniazid (INH). Therefore, early case-finding is particularly important before the development of the complex problems added by excavation. Drug regimens for tuberculosis are rapidly changing. Currently the regimen of choice is INH, 10 mg. per kilogram per day given in 3 divided doses with PAS, 8 to 12 Gm. per day divided into 4 doses and given after food. Luntz and Smith,[105] following the observation that reducing substances were present in the urine of 5 of 24 tuberculous patients on INH therapy, studied the influence of INH on carbohydrate metabolism through oral glucose tolerance tests in 6 diabetic and 6 nondiabetic tuberculosis patients. They found that INH produces a temporary elevation of the blood sugar level and both the rise and the fall of the peak are slower. It may be relevant that the glucose tolerance test in vitamin B deficiency is similar. Luntz and Smith[105] presented 2 cases to support their feeling that diabetics on INH are more difficult to control. It is wise, especially in view of the frequency of diabetic neuropathies, to give 50 to 100 mg. of pyridoxine daily to diabetics receiving INH. Hospitalization for at least two months for standardization and observation in regard to toxic drug reactions is advocated by Cooper and Marshall.[92] They recommend SM, 1 Gm. intramuscularly twice or three times a week unless pneumonic tuberculosis or extreme toxicity is present when they recommend 1 Gm. daily until fever subsides. They give 3 Gm. of PAS 4 times daily with meals and milk and caution re nausea, vomiting, diarrhea, and dermatitis with fever. It is unacceptable to administer a single tuberculostatic drug because of the rapid development of bacterial resistance under such circumstances. Antimicrobial therapy is continued for 18 months to 2 years as with nondiabetics.

Modified bed rest with bathroom privileges is still important according to Cooper and Marshall[92] and, if the patient is very toxic, they advocate absolute bed rest.

Nutritional factors are important in the therapy of either tuberculosis or diabetes and are of special significance in the management of the combined diseases.[106] Getz and associates,[107] in a study of 1,100 persons, found that ascorbic acid and vitamin A levels were markedly substandard before the development of active tuberculosis. Vitamin A deficiency in diabetics has been repeatedly emphasized. Brazer and Curtis[108] found biophotometric readings suggestive of vitamin A deficiency in their diabetics despite blood carotene levels consistently above normal. Kimble and others[109] studied the plasma vitamin A and carotene of 116 unselected diabetics. They found all possible deviations from the normal

range in vitamin A—carotene relationship, predominantly both low vitamin A and low carotene. The least frequent observation was high carotene with low vitamin A, so widely assumed as a characteristic finding in diabetes and attributed to an inability of the diabetic to derive vitamin A from the provitamin carotene. Schneider and Widman[110] explained hypovitaminosis A in diabetics as due to a close association between vitamin A metabolism and glycogen metabolism in the liver so that, with the disappearance of hepatic glycogen in uncontrolled diabetes, there was interference with the synthesis of vitamin A. Rabinowitch[111] found carotene values above normal in 85 per cent of 500 diabetics. Ralli and co-workers[112] found higher fasting blood carotene levels in 8 of 9 diabetics than in 9 nondiabetics. Administration of carotene in oil and carrots resulted in a more prompt and higher more sustained rise in the diabetics. The blood sugar bore no relationship to the blood carotene. They hypothesized that the increased concentration of carotene in the livers of diabetics is due to diminished ability to convert carotene to vitamin A and that this increased concentration of liver carotene interferes with the absorption of carotene from the blood. Banyai and Cadden[96] recommend 150,000 to 200,000 units of vitamin A daily for tuberculous diabetics.

So far as diet is concerned, underweight diabetics should receive caloric intakes calculated to raise them gradually to or slightly above standard weight. No drastic efforts should be made to reduce obese patients until toxicity has subsided[92] and the tuberculosis has stabilized, at which time they may cautiously be reduced almost to standard weight. McKean and associates[83] reported the average diet for their diabetic tuberculosis patients as 2,121 calories with 1.17 Gm. per kilogram or protein (P), 108 carbohydrate (CHO), and 135 fat (F). Reaud[84] gave his patients a 3,000 calorie diet with 150 P, 300 CHO, and 130 F. Of his 38 diabetics, 34 were markedly below standard weight on admission; 5 as much as 40 pounds under standard weight. Gais[100] uses the following ranges: 90 to 100 P, 180 to 220 CHO and 80 to 100 F. Cooper and Marshall[92] advocate a high-protein diet and require 3 glasses of milk as a daily minimum. If diabetes is out of control or the patient is quite ill, they begin with 4 equal feedings at regular intervals, covering each with regular insulin. This regimen allows the control of diabetes through gradual increase of insulin. When the diabetes is well controlled, they shift to 3 equal feedings and one of the intermediate acting insulins, either alone or in combination with regular insulin at breakfast. Fractional urine tests for sugar and 2-hour postprandial blood sugar tests are advocated until the diabetes is well controlled.

Hypoglycemia is more to be avoided than mild glycosuria, according to most authors. Banyai and Cadden[96] found that those whose blood sugars were not allowed to rise above 200 mg. did as well as those whose blood sugars were kept precisely at normal levels. PZI gives more adequate control of glycosuria with fewer hypoglycemic reactions.[113] The longer acting insulins supplemented by regular insulin are widely used.[82,83,92,113]

Surgery may be used when indicated, provided diligent search is made for complicating cardiovascular disease which is often present at younger ages among diabetics. Root[79] reports that Overholt did 23 lobectomies and 7 pneumonectomies on his tuberculous diabetics.

Prognosis.—The outlook in diabetic tuberculosis has been grave. Wiener and Kavee[91] stated that 62 per cent of their 218 diabetic tuberculosis patients died within 2 months to 6 years. On the other hand, Gais[100] reported 5-year mortality rates on 100 tuberculous diabetics at Montefiore Hospital between 1936 and 1941 to be 24.2 per cent compared to 22.9 per cent for nontuberculous diabetics. The prognosis of the tuberculous diabetic is usually that of the tuberculosis alone.[83, 84] Before the antimicrobial era, Sosman and Stiedl[69] felt that, even with insulin, the prognosis was uniformly bad. However, Thosteson and Tibbitts[86] reported that, compared with a 70 per cent mortality rate before the antimicrobial therapy, since the availability of SM and PAS, the mortality rate for diabetic tuberculosis patients has dropped to 43 per cent. They expect a further drop now that INH and long-term therapy are being used. They point out that most of the deaths are among those who had far-advanced tuberculosis on admission. Obviously, better case-finding programs are essential.

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REASONS FOR INCREASED SUSPECTIBILITY TO TUBERCULOSIS

Physiochemical Factors.—Hyperglycemia, hypoglycemia, and acidosis may be factors in the increased susceptibility of diabetics to tuberculosis. Steinbach and associates[114] reported that 6 out of 7 dogs rendered diabetic by pancreatectomy developed tuberculosis after intraperitoneal inoculation with tubercle bacilli whereas 8 controls did not. Steinbach and Duca[115] reported that albino rats' natural resistance to tuberculosis is lowered by hyperglycemia induced by pancreatectomy. Tubercles in the hyperglycemic rats contained many more bacilli than controls. They pointed out that hyperglycemia may not be the sole cause for the change in resistance. Accompanying changes in carbohydrate metabolism are the accumulation of lipids, inability to utilize vitamins, and disturbances of other endocrines.

Peters[116] pointed out, in some remarks on diabetic acidosis, that the elevation of the effective osmotic pressure of extracellular fluid by a rise in glucose dehydrates cells. Could this be a factor in increased susceptibility to infection? DaCosta and Beardsley[117] reported that diabetic leukocytes are decidedly less active in phagocytosing tubercle bacilli, streptococci, and staphylococci than are normal leukocytes.

As far back as 1928, Long[118] pointed out that the availability of glycerol in the diabetic might be of importance in the diabetic's susceptibility to tuberculosis. In 1930,[119] discussing the cultural needs of tubercle bacilli, he said "the bacillus is surprisingly selective in its utilization of carbonaceous compounds, glycerol or a monosaccharide, preferably glucose, being practically essential. Of these, glycerol is vastly superior in supporting growth. A certain amount of free glycerol and fat, a little under 0.5 per cent, is available in the body. While the amount usually added to culture media is 5 to 10 per cent, the continuous supply available in the body means that, while at a given moment the supply is never high, the amounts reaching a site of bacillary lodgment in the course of a day through blood or lymph might compare well with the effective concentration in artificial culture. Forced feeding of glycerol to rats made them veritable culture media for tubercle bacilli."

Hormonal Factors.—Bodansky and Bodansky,[120] in 1952, stated: "It is clear that diabetes is due to one or more of the following major factors: inadequate action of insulin, excessive action of the anterior pituitary, or excessive action of the adrenal cortex. These factors may be operative in different combinations and to differing extents in various types of diabetes."

If diabetes is a disease of adaptation as postulated by Selye,[11] then perhaps the diabetic personality tends to respond to life stress with an excessive outpouring of cortisone. McNee,[121] in 1950, pointing out that wounds in animals and in patients show no sign of healing and abscesses show no granulation tissue formation during cortisone administration, warned that this effect might be disastrous on the granulation tissue barrier around an active tuberculosis lesion. Dougherty and Schneebeli[122] discussed the role of cortisone in the regulation of inflammation. Michael and Wharton[123] wrote of the delay in early inflammatory response following cortisone. Is this the explanation of the slow healing so characteristic of diabetes?

Basic studies on the enhancing effect of cortisone in experimental tuberculosis were reported by Hart and Rees[124] and Spain and Molomut[125] in 1950. Kleinschmidt and Johnson[126] and Youmans[127] reported miliary spreads in tuberculous patients treated with cortisone. Lurie and colleagues[128] stated that cortisone affects in a fundamental fashion all essential mechanisms involved in the pathogenesis of tuberculosis, increasing the growth of tubercle bacilli within macrophages despite their enhanced phagocytic activity and suppressing nonspecific and allergic inflammation. Roche's group[88] found considerable similarity in susceptibility to and type of tuberculosis between cortisone-treated and alloxan-diabetic albino rats. It seems that steroids may well be involved in the increased susceptibility of diabetics to tuberculosis. In those patients in whom diabetes is first diagnosed, at or shortly after the time tuberculosis is diagnosed, the stress associated with the tuberculosis may be the triggering mechanism for making manifest a latent diabetes.

Immunologic Considerations.—Moen and Reimann,[129] presented evidence of diminished antibody formation in diabetics. Richardson,[130] in 1933, using typhoid vaccine, showed that diabetic patients form antibodies in smaller amounts than do nondiabetic controls. In a later study he suggested that the state of cellular nutrition is more important than the level of blood sugar in determining antibody response.[132] In 1941, Bates and Weiss[132] reported delayed development of antibody to staphylococcus toxin in diabetic children. Perhaps, then, fundamental immunologic disturbances are involved in susceptibility to infection. Long,[119] in presenting a chemical view of the pathogenesis of tuberculosis, noted that acquired immunity is a poor substitute for native immunity. A guinea pig may be immunized to a certain degree against tuberculosis but an increased dosage will produce disease. On the other hand, Long points out that no amount of dosage will produce human type tuberculosis in a turtle. The turtle is actively immune. Some humans possess a high degree of native immunity but a large number have tissues which seem to furnish readily the requisites for initial multiplication of tubercle bacilli. Yet most people do not die of progressive tuberculosis. It is the hypersensitive state which makes tuberculosis fulminant.

Certainly, diabetic tuberculosis is fulminating tuberculosis. Amberson, in discussing Sosman and Steidl's[69] paper, said that tuberculosis in diabetics is exudative, rapidly caseating and resembles tuberculosis in nonimmune individuals, especially children, and in nontuberculinized adults. On the other hand, as pointed out by Gais,[100] healed primary tuberculosis is common in diabetics, suggesting no difference in native immunity. Serial tuberculin studies would be of great interest.

Nutritional Factors.—Nutritional factors are undoubtedly involved. Whether underweight is due primarily to the tuberculosis, to the severe diabetes, or to the zeal of the metabolic specialist, most diabetics with active tuberculosis are below standard weight. Hypovitaminosis A and carotinemia have been discussed under nutrition in the management of the diabetic patient.

Hereditary Factors.—Heredity may well play a role. Certainly a familial history of diabetes is important.[15,79] Kallman and Reisner,[133] in a study of 308 sets of twins, their siblings, parents, and marriage partners, showed that the chance of developing tuberculosis increases in strict proportion to the blood relationship to a tuberculous index case. They felt that resistance to tuberculosis is modified by a heredoconstitutional mechanism which seems to be multifactorial in its genetic nature. Joelson and Dolger[66] postulate a possible combined genetic trait predisposing both to tuberculosis and diabetes.

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SUMMARY

A review of the literature on diabetes and tuberculosis suggests the following summary:

1. Diabetics are more susceptible to tuberculosis than are nondiabetics. Patients with tuberculosis have no enhanced susceptibility to diabetes.

2. While tuberculosis mortality rates have dropped markedly, the rate of newly reported cases of active tuberculosis has not fallen proportionately. While this may be due to improved case-finding efforts, it may be a reflection of better therapy which allows the tuberculosis patient to live long enough to die of nontuberculous disease.

3. The prevalence of diabetes has been increasing. It is, therefore, particularly important to conduct vigorous tuberculosis case-finding efforts among diabetics, not only for their own good but to avert the maintenance of a reservoir of tuberculous infection among diabetics similar to that currently existing among older men.

4. "Diabetic tuberculosis" is a fulminating disease. Early detection is of special importance in this era when potent antimicrobial drugs are available which exert their maximal effectiveness precisely on the type of acute exudative tuberculosis characteristically found in diabetics. Once cavitation has taken place, treatment is much more difficult. Suitable case-finding programs for diabetics include tuberculin testing at the time of diagnosis of diabetes and, for nonreactors, annually thereafter. Reactors to tuberculin should receive thorough clinical and radiologic study, including at least semiannual chest x-rays. The source for infection should be carefully sought in order to be sure that susceptible diabetics are not living in intimate contact with open cases of tuberculosis.

5. Causes for the diabetic's increased susceptibility to tuberculosis are not known, but various combinations of factors involved may be biochemical, hormonal, immunologic, nutritional, or hereditary.

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Editorial

THE "RISING TIDE OF INFECTION" OF SYPHILIS

For the past year or so there have appeared in the lay press scarehead articles dealing with "serious outbreaks" of venereal disease, especially syphilis, "in all sections of the country," "the rising tide of infection" especially among teen-agers and young adults, and the necessity of increased expenditures to meet this "grim" situation. One of many such examples is the *Reader's Digest* condensation of an article in the New York Herald-Tribune.[1]

There has just been circulated in mimeographed form "A Joint Statement" (presumably prepared for Congressional Committees considering Federal appropriations for venereal disease control) by The Association of State and Territorial Health Officers, The American Venereal Disease Association, and The American Social Hygiene Association, entitled, "Today's VD Control Problem: February, 1957." This document contains a number of interesting and carelessly interpreted epidemiologic statements, especially as to syphilis.* Among these are: "In 1956, *infectious syphilis* and total syphilis *increased nationally* for the first time in eight years."† The data on which this statement is based appear in an added Appendix 1, Table 1.

This table does not bear out the textual statement as to an increase in infectious syphilis. Instead, it is shown that there was an *increase* of 241 cases of certainly infectious (primary and secondary) syphilis reported by state health departments among the civilian population of the United States in 1956 over 1955; a *decrease* of 1,439 cases of potentially infectious (early latent) syphilis; and therefore a net *decrease* of 1,198 cases of actually or potentially infectious syphilis. In terms of case rates per 100,000 population, primary and secondary syphilis remained unchanged at 4.1, and these combined with early latent syphilis *decreased* from 17.5 to 16.4.‡

There was an *increase* of 20 cases of reported congenital syphilis in 1956 (from 1955) in a population of approximately 170,000,000 civilians, but the rate per 100,000 population remains unchanged at 3.4.‡

In late latent and late syphilis (all noninfectious except in women in the childbearing age), there was an *increase* of 5,110 cases in 1956 over 1955; and it is this fact which justifies the statement that "total syphilis increased nationally." Emphasis is not laid, however, on the fact that these 5,110 cases were first *discovered* in 1956, that all of them (having late syphilis) had existed before 1955,

*In so far as the "Joint Statement" refers to the minor venereal diseases—gonorrhea, lymphogranuloma venereum, granuloma inguinale, and chancroid—the remarks which follow here are not pertinent. It should be noted, however, that no noteworthy progress has been made, or is in sight, in the control of gonorrhea; and that the other three infections, never very common in this country, are decreasing in incidence for reasons unknown.

†Italics in this sentence mine.

‡The population base for these data is not provided, and it is not clear on what year's enumerated or estimated population the calculations are based.

and most of them in still earlier years, and that their discovery in any one year does not represent an increase in incidence as contrasted with prevalence.

Indeed, as has often been pointed out by epidemiologists, syphilis constitutes, for public health purposes, not one but two diseases. Early syphilis is infectious, and its incidence must be controlled if possible. Late syphilis is not infectious (except to the fetus of a syphilitic mother); and is a totally different problem in public health, analagous to those of cancer, heart disease, arthritis, rheumatism, etc. An effort must continue to prevent it, by the treatment of early syphilis, and to treat it when it is discovered.

As to early infectious syphilis, the "Joint Statement" presents an incomplete picture, since comparative data by years are given only from 1948. It is possible, however, to go back a little earlier; and this has been done by Moore,[2] from whom the following paragraphs are quoted and the accompanying figures are reproduced:

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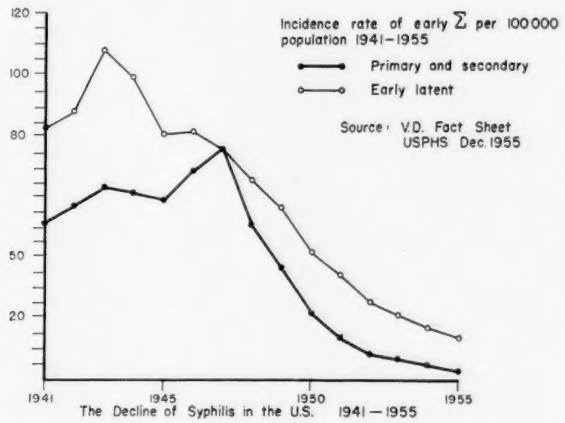

Fig. 1.

The decrease in fresh infections, i.e., early symptomatic—primary and secondary—and early latent syphilis, has been most dramatic since 1947. An accurate breakdown by stage of infection was not available in the United States until about 1941. Since then, the incidence of fresh infections is fairly accurately known. The data regarding early syphilis, now recorded as incidence rate per 100,000 population, are shown for a somewhat longer period—1941-1955—in Fig. 4 [reproduced here as Fig. 1].

Early syphilis reached a peak in 1947, when 106,539 cases of primary and secondary and 107,767 of early latent syphilis were reported. This was a typical post-war peak; of a type observed in each of our earlier wars.[3] The first 2 or 3 years of decline beginning in 1948, could have been, and was by some observers, interpreted as probably due to the usual post-war regression to pre-war levels of incidence or somewhat below. However, the fall continued, so that in 1955 there were only about 27,000 fresh infections with syphilis (6,500 primary and secondary and 21,500 early latent) in a population of about 168 million people. The 1955 incidence rates were 4 and 13, respectively, per 100,000 population.

Fig. 4 [i.e., Fig. 1. here] suggests that in 1951 the rate of decline in early syphilis leveled off fairly abruptly to something approaching stability. If these data (now in

terms of actual cases of primary and secondary syphilis) are charted logarithmically as in Fig. 5 [reproduced here as Fig. 2], the leveling off process seems much less obvious and not at all abrupt, and the decrease apparently continues.

Some epidemiological alarm has been expressed over the fact that in some states, and especially in some urban communities, there appears to be a recent reversal of trend and some apparent increase in fresh infections. Even where this is true, the increase is still slight; it is insufficient to affect the national picture and far from alarming or encouraging (whether one is alarmed or encouraged depends on one's point of view).*

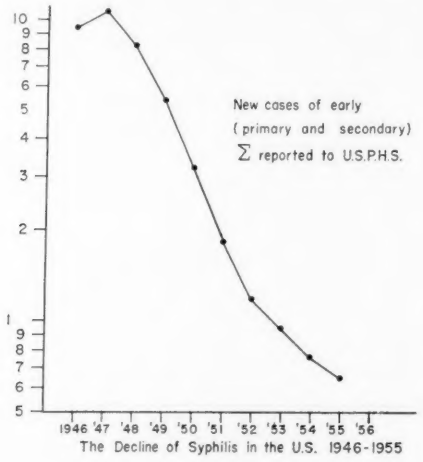

Fig. 2.

The point has been made by the "Joint Statement" (and also by Moore[2]) that reporting of fresh infections with syphilis is probably less complete, perhaps much less so, in 1950 to 1956 than it was in earlier years because of the shift of patients from clinics to private practitioners. To the extent to which this is true, the brevity and inexpensiveness of penicillin treatment is, of course, responsible. Such a shift almost certainly does not, however, account for all and probably not even for a large part of the observed decline in incidence rate.

As to the concern of the lay press and of the "Joint Statement" over the "alarming" increase of infectious syphilis among teen-agers and young adults, this seems to represent rediscovery of an epidemiologic fact well documented over many years, that the peak incidence of fresh infections with venereal disease (certainly of both syphilis and gonorrhea) is in the age group 16 to 25.

Certainly syphilis is not yet eradicated (probably it never will be in the complete sense of malaria, yellow fever, etc.); and in this country it has not yet been as adequately controlled as in some areas of Western Europe, notably Scandinavia. Certainly also, in the event of another episode of major population instability such as might be expected in (God forbid!) World War III, there will be major exacerbations, perhaps even epidemic in proportion.

*To make this semifacetious parenthetical remark entirely clear, the public health officer might be "alarmed" by such a slight increase in incidence, as indeed some such physicians apparently are. The practitioner partly dependent on fees from syphilitic patients might for selfish reasons be "encouraged" on the ground that even a slight increase presaged a return to the halcyon days of a decade ago. As a matter of actual fact neither point of view is justified by the 1956 evidence.

The progress already made, however, is substantial indeed (a drop from a peak of 214,306 cases of actually or potentially infectious early syphilis in 1947, to 26,721 in 1956). The 1956 trend is still downward, the lay press and the "Joint Statement" notwithstanding, and the statement that the "optimism [of the past few years has] proved disastrous" ("Joint Statement") seems hardly justified by the cold, bare epidemiologic facts.

Still further effort is, of course, necessary in order to maintain the gains already made and to provide a "stand-by nucleus" of venereal disease control organization in the event of a major increase in incidence from any cause. Those who seek funds from philanthropic or governmental sources, however, weaken their case, rather than strengthen it, by exaggeration and misleading interpretation of data.

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JOSEPH EARLE MOORE

Announcements

SPECIAL NOTICE

REFERENCES ON AGING FOR HEALTH PERSONNEL is a fifteen-page annotated bibliography and a four-page selected list of *books and pamphlets* which was prepared by nursing and nutrition consultants of the Chronic Disease Program of the Public Health Service's Division of Special Health Services. Single copies or limited quantities are available on request from the Chronic Disease Program, Division of Special Health Services, Public Health Service, Washington 25, D. C. Please state the title in your request.

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Since the first publication of this JOURNAL in January, 1955, several entire issues have been devoted to Symposium numbers on topics of major interest. These Symposia are usually complete discussions, which cover conflicting points of view if necessary, which often include some original work of the several authors as well as up-to-date presentation of the literature (more current than is obtainable even in recently published textbooks), and which in general may be expected to remain scientifically valid for two or more years. The Symposia are of especial value to teachers and to medical students, as well as to practitioners.

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